EXHIBIT 2D

June 1, 2012

Benjamin H. Anderson, Esq.
Anderson Law Offices, LLC
1360 W 9th St., Ste. 215
Cleveland OH 44113

Dear Mr. Anderson:

At your request, I am providing my expert opinions regarding the use of transvaginal non-absorbable synthetic mesh for pelvic organ prolapse (sometimes referred to herein as "POP") including the Gynecare Prolift Pelvic Floor Systems (hereinafter "Prolift"). The following represent my opinions, all held to a reasonable degree of medical and/or scientific probability. These opinions are based upon my background, training and experience as well as the totality of available data from all sources that I have reviewed. The following is a summary of my opinions that I have formed. I reserve the right to supplement any of my opinions based on any additional information or discovery provided and/or disclosed.

Best Regards,

Prof. Dr. Med. Uwe Klinge

Expert Report Prof. Dr. Med. Uwe Klinge

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1) BACKGROUND AND QUALIFICATIONS

With regard to my medical training, I attended medical school in Aachen, Germany from 1977 to 1983. I began my medical profession at the surgical department of the University Hospital of the RWTH, Aachen, Germany (Department heads/Mentors: Prof. Reifferscheid - 1985, Schumpelick 1985-2010, Neumann 2010). From 1995 to 2006, my practice was focused primarily on abdominal surgery, and specifically, hernia repair. As a hernia surgeon, I used textile implants (flat meshes) for the repair of abdominal wall hernia or defects in more than 300 patients, mainly groin hernia, umbilical hernia, incisional hernia and parastomal hernia. I never performed surgery for repair of SUI or POP, and never used any of the implants developed for pelvic floor.

In 1993, in addition to my surgical practice, I began focussing on surgical research in the area of biomaterial science. I am the author/co-author of 190 peer-reviewed publications listed in PubMed, 100 of which involve hernia and/or surgical mesh. I have authored and/or contributed to more than 50 book chapters and have been an invited lecturer to more than 150 speaking engagements/conferences. I have received numerous research grants from various institutions and corporations including several grants from the German Ministry for Education and Research, the Ministry for Economics, the German research foundation DFG, the NRW Ministry for Education and Research, the Interdisciplinary Center for Clinical Research of the University (RWTH), as well as from industry (Ethicon, Covidien). (Attached hereto as Appendix "A" is a current copy of my *Curriculum Vitae with a list of my publications).*

2) BRIEF HISTORY OF TEXTILE MESHES FOR TISSUE REPAIR 1958-1993 – THE ABDOMINAL WALL

The current use of textile implants, so-called meshes, is based on Usher who, in 1958, started to publish the successful reinforcement of abdominal wall in six dogs and subsequently its use for closure of abdominal wall and thoracic tissue defects, as well as for large hernia defects. In the 1960's and '70's, several procedures were developed, mainly by French surgeons such as Rives, Stoppa, Chevrel and Flament. Whereas at that time meshes were regarded an alternative, particularly in big or giant hernias, it was in 1986 that Lichtenstein presented his procedure of mesh implantation as the new standard for groin hernia repair. With this technique, the mesh reinforces the tissue in a so-called "tension free" manner which was in contrast to the forced approximation of tissues by conventional suture repairs. In the early 1990's, the use of meshes was adopted by the emerging laparoscopic TAPP (transabdominal preperitoneal prosthesis) or TEP (total extraperitoneal prosthesis) and provided excellent results regarding recurrence or postoperative side effects.

In the early years, Usher used a woven mesh made of polyester but rapidly changed to a knitted structure of polypropylene, later on widely known as Marlex®. However, Marlex® had increased stiffness after implantation and sometimes considerable local wound complications, seroma formation, infection and stiff belly. Alternatives to Marlex were the polyester mesh Mersilene® or the ePTFE from Gore.

In the early '90's, the mesh-free *Shouldice* procedure had become the standard technique for suture repair of the groin hernia, but prosthetic mesh, including "tension free" Lichtenstein repair or laparoscopic TAPP/TEP, seemed to be emerging as promising alternatives. For treatment of incisional hernia, suture repair with doubling of the fascia (according to *Mayo*) was regarded as the standard technique, but because of high recurrence rates, alternatives to such traditional procedures with mesh reinforcement seem to be a promising option. During this time, there was an intense dispute between protagonists of suture techniques and mesh techniques. Suture techniques seemed to have increased recurrence rates. Mesh techniques seemed to have lower recurrence rates but some concerning side effects. To specify the advantages and disadvantages of the specific techniques, an intense discussion started about the indication, the technique and the material.

This dispute was impeded by the rapidly evolving procedures and the general lack of knowledge about the materials and about the clinical outcome. Side effects often manifested with a considerable delay of up to several years. Correspondingly, reports dealing with pain as a major postoperative complication (less than 10% of all hernia publications in PubMed) were published with a delay of years [Fig.1].

As even the most experienced surgeon cannot avoid recurrence in all cases, the common feeling amongst abdominal surgeons was that we needed additional support for our hernia repair patients who obviously have an increased, specific risk for this complication. We therefore began to look at the scar formation pathologically and developed the theory that these incisional hernias perhaps were not, in all circumstances, the result of poor surgical technique, but rather, could be due to a biological problem.

3) DEVELOPMENT OF THE FIRST LARGE PORE MESH CONSTRUCTION THAT WAS ADOPTED TO PHYSIOLOGICAL REQUIREMENTS

In December 1993, I had to prepare a talk about "mesh" at a conference on inguinal hernia, supported by various manufacturers of meshes. In preparation for this presentation, I met with an engineer, Dr. Boris Obolenski. We began to ponder about the mesh as a textile, and the question was raised: "How strong do hernia meshes have to be?" Though the prevailing school of thought at that time was "stronger is better", we felt that we had to address this question before proceeding. Eventually, we found some references in the literature and made some of our own calculations, and finally, we estimated a required tensile strength of a mesh of about 16 N/cm. Because the market leader at the time, Marlex® (C.R. Bard) was obviously much stronger, we speculated that an adaptation of the strength to the physiological requirements may allow a considerable material reduction and may improve the biocompatibility. We felt that the textile characterization of meshes at that time did not sufficiently reflect the physicochemical properties of the textile, so we had to start almost from the beginning to first identify the relevant parameters.

I gave my presentation in February 1994 (published in Schumpelick/Wantz "Inguinal hernia repair"; Karger) stressing that we did not have sufficient data to relate the mesh properties to biomechanical demands, but that we should look for textile constructions designed specifically for the purpose of reinforcing the abdominal wall tissues. A search of the relevant literature gave

no explanation as to why the different, available meshes at that time had a particular construction/weave, strength, elasticity, amount of material/weight or polymer.

After this conference, I prepared a draft protocol for a project with the primary objective being to find a textile construction that was better adapted to the physiological requirements of the abdominal wall or groin and thus showed an improved biocompatibility. In meetings with a number of other interested research partners, we formed an interdisciplinary working group consisting of an abdominal surgeon, a pathologist, engineers, and physicists. As it was essential to find a manufacturer who was willing to provide the filaments, we presented the draft to several manufacturers, and ultimately, Ethicon agreed to join this project and provide the filaments and the currently-available mesh structures for comparison.

In parallel, RWTH University initiated a research program such that in conjunction with these grants, we could add some basic investigations to this project. Through the joint work with Ethicon and the support by research grants, the project went on for about 10 years. In this period, we gained significant knowledge about the textiles; we defined some standard biomechanical characterization for better comparison; we established models for testing the tissue response in animals; we looked for parameters that reflected the inflammatory and fibrotic activity of the foreign body reaction; we developed a technique to quantify the biomechanical impact on the abdominal wall stiffness (3D stereography); and, we measured the biomechanical properties of tissues.

As our research progressed, we calculated that hernia meshes needed a tensile strength of 16 N/cm and an elasticity of about 20-30% at this strain [Fig. 2]. Ethicon provided our research team with thin (about 40 µm) polypropylene threads. Because we were provided only with these 40-µm fibers, we had to combine 5 strands of them at interval distances of 2-3 mm to withstand a strain of 16 N/cm. As this polypropylene net was very floppy, we added an absorbable fiber of Vicryl® (Ethicon) to temporarily make it stiffer. After absorption of the Vicryl®, there would remain just an open structure, with about 30% of the material of the Marlex®. This new structure with pores larger than 2 mm, later marketed as Vypro® by Ethicon (1998) was then studied extensively in several experimental studies. The results were presented at several conferences and most of it has been published in PubMed-listed journals.

In parallel with this work, we worked on certain clinical aspects of hernia mesh implantation by improving our surgical technique of mesh implantation, analyzing the patients' scar formation to identify "bad healers", following up with our patients to check our results (in particular whether there was objective and subjective improvement by using the new Vypro® mesh), and looking for the molecular biological regulation of the inflammatory foreign body reaction.

In the 1990's, the mesh proponents at the time were convinced that the problem of recurrence had been solved, that the outcome was not affected by the type of material used and that mesh-related complications were essentially nonexistent but occurred mainly as a result of surgical technique or patient co-morbidities.

However, our work from the years of hernia mesh research with Ethicon refuted these opinions, and could prove that use of meshes designed for hernia treatment lead to an improved outcome. Here were our major findings:

1. Polymers:

i. Polypropylene and polyester show degradation with surface damage after incorporation into the surrounding tissue (i.e., they are not inert); and,
ii. Polypropylene and polyester should not be placed in direct contact to the intestine, as this can cause erosions with enterocutaneous fistula.
iii. Polivincylidenfluoride PVDF is more resistant to degradation than polypropylene PP, Polyester Pet, or Polytetrafluorethylene PTFE.
iv. PVDF induces less inflammation and fibrosis than PP or PET, indicating an ameliorated inflammatory foreign body reaction FBR
v. PVDF can be used in filaments as pure PVDF (not necessarily as blend) without additives

2. Biomechanics:

a. Strength

i. Many meshes had been designed as too strong ("over engineered") when compared with the physiological requirements; and,
ii. For large incisional hernias, a tensile strength of 32 N/cm seems to be more appropriate than 16 N/cm. For example, following implantation with Vypro®, several mesh ruptures occurred when the size of the hernia would not allow the fascia to close.

b. Elasticity

i. Due to the fabrication/design of the material, textile meshes showed a considerable anisotropy with reduced elasticity in the direction of the filaments;
ii. Elasticity or "stretchability" of a mesh usually is a consequence of deformation of the pores as the filaments do not show any elastic behavior;
iii. Elasticity or "stretchability" of meshes occurs as a result of deformation of pores, making them longer but narrower, thereby reducing the area of large pores; and,
iv. Uniaxial testing is hardly sufficient to characterize textile meshes, as most characteristics show anisotropic behavior.

c. Structural Stability

i. Loose cross-linkage of the filaments can result in insufficient stability when stressing perpendicular to the direction of the filaments (insufficient subsequent tearing force in one direction), which favors central mesh rupture (as was later seen with Ultrapro®).

3. Biocompatibility:

a. Porosity

i. Large pore is not necessarily related to lightweight and large pore is much more important than lightweight;
ii. Measurement of textile porosity does not necessarily reflect large pores. For example, in the case of small pores with thin filaments, you may have high textile porosity despite lacking large pores sufficient to resist fibrotic "bridging";
iii. The small pores of meshes lead to bridging of scar tissue from one filament to another embedding the mesh in a rigid "scar plate";

iv. Excessive amounts of material with small pores leads to intensified inflammation and fibrosis, making large pore size by far the most important mesh design characteristic for proper biocompatibility ("large pore concept"). Intense inflammatory response and fibrosis, as well as shrinkage, is responsible for chronic pain in many patients with such complaints/symptoms; and,

v. Apart from the impact of the material or the impact of the indication, patients who require removal of the mesh reveal patient specific differences in their tissue reaction in terms of intensity of inflammation or fibrosis; however, on the mean, small pore meshes show more inflammation and fibrosis than large pore meshes;

b. Tissue Integration/Foreign Body Reaction

i. The extent of contraction or "shrinkage" of the mesh area was related to the body's host inflammatory response to the mesh;

ii. Wound contraction leads to shrinkage of the device area and can thereby lead to considerable folding of the device and associated pain, sometimes chronic in nature;

iii. Folding ("curling" or "roping") of a device usually as a result of strain, leads to local accumulation of polymer and increases the inflammatory response; and,

iv. The addition of Vicryl leads to stimulation of inflammation and fibrosis.

4. Complications

i. Increased surface area of multifilament mesh may be related to increased adherence of bacteria and thus, a higher risk of infection;

ii. Our analysis of explanted mesh showed that most of the meshes had to be removed at a mean of 2-3 years after implantation due to complications of infection, recurrence and/or chronic pain; and,

iii. In the long term, about 5% of meshes used for repair of incisional hernia have to be removed mainly (60%) because of infection.

5. Optimal Design

a. Widely-accepted design requirements for hernia meshes today are 1) large pore construction (>1mm in all directions) to reduce inflammatory foreign body reaction, 2) monofilament to reduce bacterial adherence, 3) tensile strength of about 16 N/cm (groin) or 32 N/cm (incisional hernia), and 4) some elasticity may be favorable (no agreement because of differences in localization, application and fixation).

To conclude, through our work with Ethicon in the mid to late '90's, our research team was able to determine that an implantable surgical mesh device which is properly designed for its intended purpose of reinforcing the abdominal wall tissues for the repair of groin hernia and of incisional hernia should have a construction adapted to the physiological demands of the abdomen/groin with reduced amount of material, large pores, adequate strength and elasticity. Such a mesh design showed beneficial and increased biocompatibility in comparison to stiffer "heavyweight" materials with small pores and inappropriate strength and elasticity. Still today, almost 15 years after introduction of the first large pore mesh, Vypro®, there is no reasonable clinical or experimental evidence that meshes should be stronger and more flexible/elastic.

4) MAJOR DESIGN PRINCIPLES TO BE CONSIDERED BY MEDICAL DEVICE MANUFACTURERS OF SURGICAL TEXTILE IMPLANTS IN THE PELVIC FLOOR

As a result of our work in developing the next generation of surgical meshes as well as the significant world-wide research and development of countless others over the past almost two decades, we have learned that the development of an optimal surgical mesh design for any application has to consider first, the polymer; second, the biomechanics (physiological requirements) as to strength, elasticity and structural stability; and third, the structure of the device in terms of geometric design, knitting characteristics, fiber size and pore size. The result of these design considerations and choices will influence the tissue reaction, primarily the intensity of the inflammatory and fibrotic response, thereby directly affecting the biocompatibility of the device and thus the clinical outcome regarding potential complications such as chronic infection, chronic pain, erosion, shrinkage, migration and recurrence [Fig. 2]. These principles apply somewhat equally, with a few distinct variations, to hernia mesh as well as to pelvic mesh.

a. POLYMER

When designing a surgical mesh, the manufacturer must first decide which material to use. The choice of which textile material to use will depend upon the intended function of the device and the area of the body in which it will be implanted. An extension of this choice of material will be the design consideration of how the body will react to a certain polymer and thus, whether there will be any unintended consequences that could increase the risk of injury to the patient, thereby making one choice of polymer safer than another.

Nearly all non-biologic, alloplastic mesh materials on the market today are comprised of one of four polymers: polyethylene terepthalate or "polyester" (PET), expanded polytetrafluorethylene (ePTFE), polypropylene (PP) or polyvinylidene fluoride (PVDF).

PET (polyester)

Polyester is a macromolecular compound. The major disadvantage of polyesters is their tendency to degrade in the human body via hydrolysis. After several years, polyester grafts lose most of their mechanical stability due to hydrolytic splitting of the polymer. This process may even be accelerated in the presence of infection. In 1998, Leber and colleagues [1] found significantly more infections, recurrences and fistulas after use of polyester meshes for incisional hernia repair, and, therefore, they concluded that the mesh should not be used for hernia repair. Pubovaginal polyester slings have also been associated with increased risk of infection and fistula formation, one of which, the ProtoGen sling (Boston Scientific), was withdrawn from the market in 1999.

PTFE

PTFE and ePTFE are film-like sheets characterized by tiny pores of 1-6 µm. They cannot be penetrated by scar tissue and, therefore, induce the encapsulation of the entire

prosthesis. Not only are these polymers prone to insufficient integration into the surrounding tissue, they also lack long-term stability. Bellon et al. [2] found alterations to the ePTFE structure such as areas of fragmentation, fracture lines and detachment of the fine layers in the presence of infection. Small particles of ePTFE were found to be detached from the surface, which was then found to be phagocytized in macrophages colonizing the interface. Implants made of these polymers show decreased physiologic elasticity once incorporated into the host tissue. The infection rate following sling procedure has been reported to be up to 2% with up to 16% of patients complaining of varied amounts of pain at the implantation site.

PP

Due to the disadvantages of both PET and PTFE/ePTFE, PP emerged as the most widely-used material for both hernia and pelvic floor repair. In fact, of all the non-absorbable synthetic mesh products for urogynecologic indication cleared by FDA, 91% are PP. [3]. As such, PP is currently the most utilized synthetic surgical material. It is a thermoplastic prolene material with a melting point at 160°C (320°F) and a molecular weight of 100kD. Measurements of the yarn tension of PP-suture material have shown a 50% tension decrease after seven years under hydrolytic conditions. Additionally, it has been suggested by numerous authors that PP is susceptible to oxidation/degradation, resulting from exposure to strong oxidants such as hydrogen peroxide and hypochlorous acid. (*See* "Complications" section below for further discussion of PP degradation)

PVDF

PVDF is a nonabsorbable flouropolymer, consisting of alternating methylene and diflouromethylene groups. Studies have shown that this polymer has improved textile and biological properties. It is thermally stable and more abrasion resistant than other flouroplastics. PVDF sutures are routinely used in cardiovascular and orthopedic surgery. It is said to induce a minimal cellular response, to show exceptional chemical stability and to have excellent resistance to aging.

Ethicon's development of PP mesh

Ethicon's use of PP as a suture material dates to the late 1960's when it began purchasing PP resin for its Prolene sutures from the Montecatini Company at their Novamant Plant in Kenovah, West Virginia. The mixing and compounding of the resin has not changed since that time – same composition; same molecular weight; and same molecular weight distribution. The individual component additives to the resin are Santonox (an antioxidant that is intended to prevent thermal oxidation during extrusion); calcium stearate (lubricant); dilauralthiodipropionate (another antioxidant intended to reduce effects of long-term storage); Procol LA-10 (another lubricant intended to reduce tissue drag and promote tissue passage); and CPC pigment (colorant to enhance visibility). After the extruded resin material leaves the compounder, it is water quenched, pelletized and airveyored to polyethelene drums for shipping to Ethicon. [4]

Prolene sutures were developed into a flat hernia mesh in 1975 (Prolene mesh) and as 3-dimensional form in 1997 as the Prolene Hernia System, each consisting of a heavyweight,

monofilament, PP hernia mesh. Ethicon then extended the Prolene line by developing Prolene Soft mesh which was cleared for marketing in the U.S. in 2000. That same year, the FDA cleared Vypro for marketing in the U.S. as well. As mentioned above, I was part of the outside research team working with Ethicon to develop Vypro, a lightweight, multifilament, PP hernia mesh with an absorbable component, polyglactin-910.

Then, in 2002, Ethicon repackaged its Prolene Soft mesh as Gynemesh PS and received clearance by the FDA to market it in the U.S. in 2002 for pelvic floor repairs. It was the same mesh material as the hernia mesh, Prolene Soft, and was the first pelvic mesh cleared for marketing in the U.S. for treatment of pelvic organ prolapse.

FDA cleared another Ethicon hernia mesh in 2004 with the trade name of Ultrapro. Ultrapro is made of monofilament PP fibers with interwoven absorbable Monocryl fibers

In 2005, Ethicon marketed and sold a new pelvic mesh kit, Prolift. Prolift is the same identical mesh as Gynemesh PS and Prolene Soft hernia mesh but is precut and packaged with surgical tools for placement of the mesh, and inserted pursuant to the Prolift procedure.

In sum, from 1997 to the present, Ethicon's marketing efforts in the U.S. for its surgical meshes for both hernia and pelvic floor application have remained focused on PP as the polymer of choice for these products.

Claims by Ethicon

Over the years, in relation to the manufacture and sale of its PP surgical mesh products, Ethicon has repeatedly claimed in its communications with regulatory bodies, its communications with doctors and patients, and its internal corporate documents (i.e., design verification, etc.) that PP, as a surgical material, is safe in the human body due to its identical composition of a Prolene suture (e.g., In the 510(k) submissions and IFUs, Ethicon states that these surgical mesh products are "constructed of knitted filaments of extruded polypropylene identical in composition to Prolene Polypropylene Suture, Nonabsorbable Surgical Sutures, U.S.P. (ETHICON, INC.) This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. This language is also repeated in the DDSA for Prolift [5,6] and the Gynemesh PS "White Paper" [7]

In fact, the Gynecare Prolift IFU specifically states that the PP material in Gynemesh PS is not "subject to degradation or weakening by the action of tissue enzymes." [8]

Degradation

Studies as early as the 1970's and 1980's demonstrated concern over the degradative effects of polypropylene when used in the human body. [9,10] It was presumably due to such concerns that Ethicon adds anti-oxidative additives to its compound batches when formulating and extruding the PP resin at its plant in West Virginia – a process that has barely been revisited, retested or changed since the late 1960's.

More recently, there has been growing concern regarding the degradation of PP in prosthetic mesh implants. It is believed that oxidation of the mesh occurs as a result of the chemical structure of PP and the physiological conditions to which it is subjected. This leads to

embrittlement of the material, impaired tissue mobility and eventually chronic pain. Some authors feel that heavyweight PP fibers incite a greater inflammatory response than lighter weight fibers and thus undergo greater oxidative degradation. Costello reported in 2007 that certain by-products of the inflammatory process, namely, hydrogen peroxide and hypochlorous acid, causes the PP to more susceptible to the oxidative effects of the metabolites produced by phagocytic cells during the inflammatory response. They saw cracks and other surface degradations such as peeling of the PP fibers under Scanning Electron Microscopy (SEM). [11]

It was believed for decades that PP is inert. This belief is only partly true. However, many studies have demonstrated that PP is not biologically inert and, for purposes of determining whether PP is the optimal polymer to be utilized as a surgical implant in the human body, this latter characteristic is much more important. Clave performed a comparative analysis of 100 pelvic mesh explants. The average period of removal was 790.6 days. Over 20% showed such degradation damage to the fibers. [Fig. 3] The article states that the lead author of the study had an educational position for Ethicon Europe. [12] Other authors have also written about the degradative effects of PP in the human body. [13, 14, 15]

The clinical implications of a degraded, oxidized surface of PP mesh fibers in human tissue are not completely known. Such degradation, depending upon the severity, can lead to a "barbed wire" effect whereby the peeled surface fibers create an enhanced inflammatory tissue response due to the lack of a smooth surface coming into contact with the tissue. Obviously, the mesh is not at rest after implantation -- quite the contrary. As a result of the inherent nature of the physiological forces and stresses being placed on the prosthetic after implantation, the mesh will move and stretch in an anisotropic manner in the tissue. This frayed surface can damage the tissue in which it is implanted leading to an increased host defense response at the tissue/implant interface.

Furthermore, the cracked and frayed fiber increases the surface area of the mesh. Increased surface area causes a more intense foreign body reaction and thus, a greater inflammatory/fibrotic response.

Finally, bacteria are more likely to lodge in the cracked areas of the fiber surface in vivo thereby increasing the risk of infection which would also create a greater host defense response.

It is important to note that Ethicon hired an outside consulting firm, PA Consulting Group, to analyze its surgical mesh for the pelvic floor. In an extensive report, dated May 18, 2011, PA Consulting opined that "Polypropylene can suffer from degradation following implant….a process which initiates after a few days post implantation in animal studies." Numerous reasons are listed as possible causes of such degradation. In fact, one of the clinicians that PA Consulting interviewed when collecting data for the report "proposed that variability in the raw materials, and/or processing thereof, could be affecting the clinical performance and outcomes. He articulated his intention to investigate this hypothesis." A collection of "high resolution images of excised meshes clearly show physical degradation of polypropylene filaments." The report states that these images were collected from Prof. Klosterhalfen, but rather than include them in the report, PA Consulting says that the images are "on file". [16]

Although it is unclear when Ethicon was provided these images depicting clear degradation of the explanted PP fibers from Prof. Klosterhalfen, certainly degradation of PP in

the human body has been the subject of scientific journals for decades and within the last few years, PP degradation when used as surgical meshes has been the subject of a number of articles as well (one of which being authored by an Ethicon consultant) as a hot topic over a year ago by their outside consulting group. Therefore, it is curious that this information was known or knowable by Ethicon yet they claim to the FDA, surgeons and patients that the PP material in Gynemesh PS and thus, Prolift is not "subject to degradation or weakening by the action of tissue enzymes."

In my opinion, it has been proven to a reasonable degree of scientific probability that surgical mesh made of PP and used in the pelvic tissues is not biologically inert and does in fact undergo degradation at the surface of the mesh fiber leading to an increased host inflammatory response. Therefore, Ethicon had a duty to test the potential degradative effects of the body's reaction to the PP mesh used in Prolift in order to determine whether the anti-oxidants that it has been using for some decades does, in fact, prevent surface cracking and peeling of the mesh fibers in the human tissue. According to their outside consulting group, they do not.

It was inappropriate, false and misleading for Ethicon to claim that their PP meshes were not subject to degradation. In fact, Piet Hinoul, Ethicon's WW Medical Director in a 2009 presentation "[modern day meshes] are not biologically inert". [16a]

Fibrotic Reaction

PP filaments cause an intense inflammatory response in the abdominal wall as well as the tissues of the pelvic floor. There is increased fibrotic reaction which stimulates remodeling at the tissue/implant interface. This intense scar formation contributes to the wound contraction [17] (A more extensive discussion of the overall foreign body reaction to PP meshes is set forth in this report below.)

Ethicon's consideration of the degradation of PP in vivo and the body's inflammatory response to PP fibers

I have seen no studies whereby Ethicon attempted to determine the long-term, degradative effect of PP in the tissues of the human body and specifically, in pelvic tissues. Nor have I seen sufficient data from Ethicon's own internal studies whereby they evaluated the body's inflammatory response to PP fibers. A reasonable medical device manufacturer should have done so, and failure to conduct such studies increased the risk of harm to patients in whom PP mesh implants would be permanently implanted. Internal documents reveal that there was some recognition of not only the degradative effects of PP in surgical mesh but also that Ethicon's PVDF mesh, Pronova, was more elastic and demonstrated less degradation than PP. [18] However, I have seen no internal studies/testing by Ethicon in this regard.

Ethicon's consideration of alternative polymers/designs for pelvic floor repair

The primary task of biomaterials is the durable and adequate reinforcement of the tissues in which they are implanted. This requirement demands the absence of polymer degradation as well as a textile construction that prevents any functional and histological impairment. Because of the known disadvantages of PET, PTFE and PP, the introduction of new polymers seems to be advisable. This is especially true given that "the polypropylene mesh used today has largely

remained unchanged" since 1962 [19] and Ethicon's internal documents show that their PP has remained virtually unchanged since the late 1960's!

As mentioned above, polyvinylidene fluoride (PVDF) has emerged in recent years as a newer, potential, alternative polymer to PP as a surgical prosthetic to strengthen pelvic floor tissues. Ethicon themselves began testing PVDF vs. PP over a decade ago. PVDF has its origins in vascular surgery (cardiovascular and orthopedic) as a suture material that was found to have exceptional chemical stability, to induce minimal cellular response and to have excellent resistance to aging. [20, 21, 22, 23]. In fact, of the four polymers currently used for surgical mesh application, PVDF is probably the synthetic material with the best biocompatibility, the least amount of foreign body reaction and optimal ingrowth. It combines the minimal cellular activation of PTFE and the capability for the construction of porous meshes as with PP.

In July 1998, I began doing research on PVDF as a potential mesh material as a result of a granted project funded by IZKF of the Aachen University. At that time, some colleagues and I approached Ethicon Hamburg and asked if they were interested in sponsoring a study comparing PVDF mesh to PP, to which they agreed. Thus, in approximately 1999-2001, I was part of an animal study, supported by Ethicon, in which we compared the functional consequences and morphological tissue response of a common heavyweight polypropylene mesh (Prolene) to two samples of PVDF mesh, of which one was provided by Ethicon for the study. Our published as confirmed that hernia meshes made of PVDF are an advantageous alternative to the commonly-used PP materials due to improved biostability, lowered bending stiffness, and minimum tissue response. In addition, PVDF showed preserved mechanical stability even after long-term incorporation. In comparison to PET, the PVDF was more resistant to hydrolysis and degradation. Older comparator studies of PP versus PVDF dated back to the mid-1990's. In animal experiments for up to two years, there was visual evidence of surface stress cracking for PP but not for PVDF. Even after nine years of implantation, the PVDF preserved its mechanical stability with 92.5% of its original strength. In contrast, the PP sutures lost about 46.6% of their stability due to an accumulation of oxidation byproducts and water molecules near the surface. The histological examination of sutures made of PVDF after incorporation for six months in dogs showed only minimal cellular response without excessive fibrous tissue reaction. Furthermore, aging did not increase the stiffness of PVDF as it did for PP. Considering the development of bioactive mesh materials for ECM remodeling or infection prophylaxis, PVDF would be considered to be a more suitable base material than PP for these emerging products as well. [24]

Further scientific work comparing PVDF to other polymeric materials has also been done which substantiates its superior in vivo functionality and histological response. [25,26]

b. BIOMECHANICS

The main task of biomaterials used for surgical repair is to strengthen the tissue in which it is implanted and to restore its function. Specific to pelvic organ prolapse, the primary task of the prosthetic is to strengthen the pelvic floor tissues and to restore the pelvic anatomy and function. The mesh should mimic as closely as possible, and be integrated physiologically into, the tissues of the pelvic floor based on a maximum biocompatibility. Such surgical biomaterials should be

without serious long-term complications such as recurrence, infection or chronic pain, and should have optimal handling characteristics for an easy, comfortable and safe repair.

Whereas the physiological requirements of textile structures used as flat, "tension free" mesh for repair of abdominal wall defects is widely accepted, the definition of the physiological requirements for devices used in the pelvic floor is less clear, and in some cases unknown, but nevertheless required for appropriate mesh design [27]

Ethicon's professional education team communicated what it considered to be the "ideal" mesh requirements for pelvic floor repair to physicians that were being trained by Ethicon in the Prolift technique. They stated to physicians that the "ideal" vaginal graft should "be histologically well tolerated (inert), resist infection, be easily handled and implanted, incorporate into surrounding tissues, resist mechanical stretch, not shrink, and recreate and maintain the physical characteristics of the supple and distensible vaginal wall." [28]

Ethicon is fully aware of the difficulties in defining the biomechanical requirements of the human pelvis. They admit in their internal documents regarding the biomechanical requirements of the pelvis that although "…**the ideal mesh for prolapse repair which mimics precisely the biomechanical needs of the pelvic floor region has not been developed**." (Emphasis added) Ethicon recognizes that:

> a recent major focus of mesh development and research is the patient's quality of life. Pain and discomfort can result from stiff mesh that were originally designed for hernia surgery and 'over-engineered' to exceed the burst strength of the abdominal wall at the cost of losing compliance. Although limited data suggests that, in terms of anatomical and biomechanical outcomes, synthetic polypropylene meshes are superior to biologic meshes, there is significant evidence that the complications associated with synthetic meshes can cause significant morbidity including infection, erosion, exposure, and pain. In addition, the vaginal tissue to be augmented is often structurally compromised, atrophic, and devascularized. Such poor tissue quality increased the risk of poor tissue incorporation into the mesh potentially resulting in suboptimal healing and mesh exposure or erosion into an adjacent viscous. Moreover, there is evidence that meshes shrink in vivo leading to increased stiffness, pain and poor restoration of the normal properties of the vagina compliance. Research has demonstrated that bioprosthetic mesh implantation results in a scarring reaction and subsequent decreased compliance. An ideal quality of prosthetic mesh would be to mimic the compliance of the supported tissue thereby resulting in more comfort and function after implantation. To be able to define the most appropriate design parameters for the next generation of pelvic floor prosthesis it is important to generate an advanced understanding of the pelvic floor biomechanics and associated mechanical boundary conditions. [29]

As stated above, prior to the Ethicon document just mentioned, during the product development of a PVDF mesh in Project Thunder, Ethicon recognized that the main unmet need of its customers, mesh surgeons, was restoration of the natural anatomy and function of the pelvic floor and the vagina. But Ethicon further recognized that there was no pelvic floor specific mesh on the market as more research was needed regarding the poorly understood

biomechanics of the pelvic organs and pelvic organ prolapse. This lack of a pelvic floor mesh prosthetic that addressed these characteristics was one of the primary stated reasons that Ethicon was trying to develop Pronova.

Ethicon scientists recognized that the unique requirements in pelvic reconstructive surgery include the fact that 1) *anatomically*, the pelvis has a complex, 3-dimensional architecture and vector forces with little or no bony (and often pelvic floor muscle) reinforcement, and 2) *functionally*, the prosthetic must remain pliable as a result of pelvic organ filling/emptying, tissue pliability, and sexual function. [28] These and other Ethicon scientists also admitted that there is no descriptive model available to predict the mechanical behavior of pelvic mesh implants.

Other employees at Ethicon, namely, those involved in regulatory and sales and marketing, told a different story. In the Prolene Soft 510(k), the Gynemesh PS 510(k), as well as in the Gynecare Prolift IFU, Ethicon claims that "the elastic properties of the mesh adapt to the various stresses encountered in the body." Ethicon admitted to the FDA in 2007 that they had no data to support this statement. [8] In its patient brochures for Prolift, Ethicon claims that the Prolift repair system is "a revolutionary surgical technique… [that] uses a soft synthetic mesh specially designed for placement through the vagina…" [30] However, the term "specifically designed" came to the attention of Mark Yale, WW Director of Risk Management during the development of the Prolift +M IFU. He stated that "this mesh was not 'specifically designed' for Prolift application, we pulled a mesh out of our existing bag of tricks." [31]

Dr. David Robinson, Medical Director, Ethicon gave a Power Point presentation titled "Review of Surgical Techniques Using Mesh", [32]which was marked as Plaintiffs' Exhibit 519 of his deposition. The presentation states: "material science has been slow to meet the special requirements of the vaginal environment" and "The vagina is not the abdomen and it is not similar to any other surgical environment." When this portion of his presentation was discussed at deposition, [33] Dr. Robinson agreed that these are accurate statements.

Physiologic properties of pelvic tissue

The primary difficulty in developing a model to predict the mechanical behavior of pelvic mesh implants lies in the understudied and poorly understood characteristics of vaginal tissue. Drawing conclusions from studies involving animal tissues in an attempt to correlate those findings to the tissues in the human pelvis has severe limitations. As Ethicon has recognized, "[a]nimal models allow for controlled studies, which are useful in understanding the underlying factors that may contribute to the development and progression of human diseases by systematically examining confounding risk factors. However, the need to translate findings to the clinic is very important, and therefore understanding how these animal models relate to humans must be evaluated." [29]

At the conclusion of our work in the development of Vypro hernia mesh with Ethicon, my colleagues and I published an animal study in which we demonstrated that the physiological forces of the abdominal wall could be quantified. By properly defining these physiological forces for the first time, we were able to demonstrate how the animal model related to human in vivo behavior to improve the textile structure of hernia meshes, and thus, to improve the symmetrical distribution of the retaining forces in all directions. Compared with the

considerable restriction of the abdominal wall mobility by Prolene (polypropylene) and Mersilene (polyester) meshes, there was no increase in the bending stiffness after the implantation of the new mesh in rodents. Histological examination showed a pronounced reduction of the inflammatory reaction in the tissues, and the collagen bundles were orientated merely around the mesh filaments instead of forming a scar plate that completely embedded the mesh. By adapting the design of the new hernia mesh to the physiological forces of the abdominal wall, we were able to reduce the amount of prosthetic material which caused less inflammation and less restriction in the mobility of the abdominal wall while retaining the required tensile strength of 16 N/cm.

No similar, definitive studies have been conducted for the pelvic floor. Pelvic tissue is extremely complex. It has a non-linear stress-strain relationship, large deformation before yield, is viscoelastic, inhomogeneous, anisotropic and, when trying to analyze the tissues upon explant, has changing vaginal tissue properties after removal from the body. [34] Furthermore, there is no scientific consensus on a standardized test to characterize the properties of the human vagina. There have been a number of scientists and surgeons, Cosson, Rubod, Boukerrou, and Boulanger, just to mention a few, who have attempted through various studies to characterize the biomechanical behavior of human vaginal tissue. However, as is evidenced by their studies and acknowledged by Ethicon, "the reported vaginal tissue properties vary extremely for different investigators and different experimental setups; there is no consistent nomenclature for biomechanical properties established; and, the reported material parameters exhibit a strong deviation even between different patients, examined by the same investigators." In fact, although these studies are important initial steps in characterizing the biomechanics of the pelvic tissue, as Ethicon admits, "more data is needed from humans to help us characterize the differences between normal and pathological tissues, as well as to help us identify appropriate animal models." [29,34]

Unlike my work with Ethicon in quantifying the physiological forces that are placed on the tissues in the abdominal wall and working to construct a prosthetic mesh that adapts to those characteristics, it appears that Ethicon has earnestly not attempted, much less, successfully conducted, similar studies, animal or otherwise, in constructing Prolift. To the contrary, apparently Ethicon merely converted our work on new generation hernia meshes and repackaged it as pelvic meshes assuming, without justification, that a safe mesh design for hernia application equaled a safe mesh design for pelvic floor application. As injuries to numerous patients continue to mount, this assumption has proven dangerously faulty.

For example, from October through December 2008, prior to Ethicon's launch of its new generation POP mesh, Prolift +M, there were required readings by the sales and marketing force to educate them regarding certain aspects of pelvic floor meshes before detailing the product with surgeons. These were known as "Prolift +M Pre-readings". Jonathan Meek, the Prolift +M team member in charge of sales and marketing, included in these readings the work that my colleagues and I had done ten years prior (reference above). This leads me to a number of important observations: 1) Ethicon had not conducted their own studies on pelvic mesh that would have built upon the knowledge they had gained a decade prior in order to determine whether their pelvic floor approximated the physiological forces in the pelvis; 2) four of the seven suggested articles were studies involving hernia meshes from the late 1990's and only two of the remaining studies involved vaginal tissue; and 3) Mr. Meek admitted in an email dated

October 29, 2008 that "up until recently, I was ignorant to the work carried out by the likes of Cobb, Klosterhalfen and Klinge to name a few as it was assumed that they [were] primarily researching Inguinal Hernia repair and it didn't translate to Pelvic Floor. As it turns out, the vast majority of their work is pre-clinical which mirrors the more recent work done by Cosson, Boulanger, Rubod et al. done for the Pelvis." [39]

Mr. Meek's statement is actually only partly true. Yes, our work was to a large extent "pre-clinical" in order to better understand certain design parameters of hernia meshes.

However, unfortunately, our work was not continued by Ethicon in its development of pelvic meshes in that they failed to define the physiological forces in the pelvis and thus to translate this to design consideration for pelvic meshes. The work by Cosson et al. is preliminary in this regard. As Ethicon's own documents point out, there are still many unknowns regarding how best to design pelvic floor meshes in light of the still undefined physiologic requirements of pelvic floor and in particular, vaginal, tissues. As Mr. Meek points out later in his email, these studies from the late 1990's have a few key points. Two of these that he communicates to the sales force are that "PP is the best of a bad lot re integration and retraction [sic] and there is a need to develop grafts that mimic the human tissue mechanical properties… [and] the need for graft with elastic properties to match [the hyperelastic properties of the vagina]." How interesting, if not disconcerting, that on the one hand, this Ethicon employee cites the need for implants that match the biomechanical properties of the pelvic tissues yet on the other hand, he cites and provides his sales team with literature that justifies hernia mesh in rat abdominal tissues.

Unfortunately, Mr. Meek was not the only Ethicon employee who was misguided in this analysis. In May 2007, while the Prolift +M team was recommending updates to the IFU, they also attempted to use our 1998 rat study to support claims in their IFU for Prolift +M. It was disingenuous, at best, and closer to misleading for Ethicon to use a ten-year-old hernia mesh study from the abdominal wall of rats to validate their claim that Prolift +M would "illicit a minimum to mild inflammatory reaction" and "thus incorporate the mesh into adjacent tissue." They also used our study from 1998 to claim that "the bi-directional elastic property allows adaptation to various stresses encountered in the body." First of all, the mesh we used in our study was Vypro, which was a multifilament PP mesh designed for the abdominal wall. Additionally, Vypro's PP fibers were intertwined with an absorbable component, polyglactin-910. Finally, the mesh in our study was implanted in abdominal tissue, not pelvic tissue. This is quite different from the use of Prolift in the female pelvic.

The most prudent course of action by Ethicon following the development of Vypro would have been to continue to utilize the newly-developed design characteristics that reduced complications in hernia mesh patients, but to then design tests and pre-clinical studies that applied specifically to pelvic floor meshes in order to develop better and safer design characteristics that would have a better chance to reduce complications in pelvic mesh patients. Instead, what Ethicon did was to use some of the general findings from these early hernia studies to justify their later claims in submissions to FDA and in IFUs to surgeons that the various iterations of their pelvic mesh products demonstrated the same characteristics of physiological tissue adaptation in the pelvis.

Perhaps this concept of the vast difference between abdominal wall tissues and pelvic floor tissues was best and most succinctly stated by the Director of Medical Affairs at Ethicon, David B. Robinson, MD, in his 2008 PowerPoint presentation "Review of Surgical Techniques Using Mesh", when he stated "The Vagina is NOT the Abdomen (nor similar to any other surgical environment)". [32] He clearly presented that there was a "poor understanding of tissue-mesh interactions and that **material science has been slow to meet the special requirements of the vaginal environment**." (emphasis added)

However, in another unfortunate example of the internal confusion and disparity of knowledge regarding surgical mesh and specifically, the differences between the tissues of the abdomen versus the pelvis, is seen in an email by a top R&D scientist, Joerg Hoelste, when he stated in March 2007, "My thinking is that a pelvic floor prolapse is clinically comparable to hernia development, because it is part of the abdominal wall." [40]

Clearly, the scientific reality weighs in favor of Dr. Robinson's analysis much more so than Dr. Hoelste's. Ethicon has stated repeatedly in its documents that it had a very poor understanding of the biomechanics of the pelvic floor which apparently continues to this day. The problem is, of course, if the manufacturer of a permanently-implanted, synthetic device does not have a sufficient understanding of the biomechanical properties of the tissue in which the device will be implanted, nor an adequate understanding of the biomechanical forces of the area of the body in which the device will be implanted, the risk of short- and long-term complications to the patient are dangerously increased, thereby exposing patients to injury. [Fig. 4]

More recently, Dr. Daniel Elliott of the Mayo Clinical published an article stating two very obvious concerns that should have been raised: 1) "The first concern this should have raised regarding using synthetic mesh in the vagina is that synthetic meshes are not a perfect solution for abdominal wall hernias. A tremendous amount of data in the general surgery literature details a long litany of mesh complications…The second question or concern that should have been raised and thoroughly studied prior to widespread industry acceptance of transvaginal mesh kits is that the vagina is not the abdominal wall." [41]

I agree. I also agree with Ethicon's conclusions in its analysis just last year in 2011 regarding the biomechanical considerations for pelvic floor mesh design: "We have shown that currently there is an important need for animal models in pelvic floor research…Of course, we ultimately need to know what is happening in the human female…The development of knowledge to understand the mechanics of pelvic floor disorders is imperative; yet, we are only just beginning to determine the necessary criteria on which to base design for pelvic floor implants." [29] This admission by Ethicon comes 11 years after putting Gynemesh PS on the market and 6 years after putting Prolift on the market as a "revolutionary" procedure.

i. Strength

Measurements of the tensile strength of human tissue indicate a maximum strength of about 20 N/cm before rupture. Estimates of maximum physiological abdominal wall tensile forces indicate a maximum of 16 N/cm for smaller defects and 32 N / cm for larger defects. These limitations should be provided in all directions and considered as the minimal limit of the force for subsequent tearing. Although testing of sufficient tensile strength in the pelvic floor

has been understudied, one can assume that it would not exceed the tensile forces in the abdomen (16 N/cm).

The Gynemesh PS white paper similarly states that strength is an important property of synthetic meshes. It also states that "Although in vivo forces and exerted strains on pelvic floor repairs are difficult to quantify, it is unlikely that they are significantly different than those found in the abdomen. Synthetic meshes have been used for years in the repair of abdominal and inguinal hernias and have proven to be of adequate strength to provide tissue support in that region. In fact, many meshes may be over-engineered with respect to strength and mesh density and weight may be able to be significantly decreased. However, the extent of this decrease and the minimum mesh strength requirement for pelvic floor repair is not known." [7] It is not possible to design an appropriate surgical mesh if the signal environment is not understood.

Holste reported in 2005 in an article "Are Meshes With Lightweight Construction Strong Enough?" that surgical mesh must provide sufficient biological strength to meet physiological requirements without being over engineered. He added a graph to his publication showing that the maximum tensile strength on the abdominal wall is 150mmHg. The graph demonstrates that Ethicon's hernia meshes Ultrapro, Prolene Soft and Prolene all have burst strengths that are far above the maximum needed strength in light of the maximum abdominal pressure (Ultrapro = 650 mmHg; Prolene Soft = 700 mmHg; Prolene = 1650 mmHg). Holste correctly notes that over-engineered meshes (i.e., those whose strength is far above the maximum requirements of the tissue in which it is implanted thus leaving excessive amounts of foreign material in the body) lead to stiffness, excessive scar plate formation and abdominal wall restriction, all of which in turn lead to complications of reduced patient comfort and chronic pain. However, in that same article, he states that these meshes "possess adequate strength to repair the abdominal wall." He has missed the point. The question is not whether the meshes have *enough* or *adequate* strength, the question for Holste and his employer, Ethicon, should have been (and continues to be even to this day) "Do our meshes have *more* material and/or *more* strength than is required to accomplish the task of reinforcing the tissues in which they are implanted?". His conclusions thus belie a proper analysis of the data that he seeks to present given that Prolene Soft is over *four times* stronger than the maximum tensile strength of the abdomen, and Prolene is over *ten times* the required strength! [44]

Again, the main task for reinforcement by textile structures is the compensation of any tensile strength. In the case of prolapse, it should retain the pelvic floor with its organs, which means there will be tension by definition. Thus, declarations or claims by Ethicon that the Prolift Kit are "tension free" are untrue and defy scientific sense or even common sense. The bearing of forces by the textile area is much more complex and hardly possible to be calculated exactly for every part of the mesh.

However, as *Cosson* et al.[35] discovered, the vaginal tissue showed rupture at a strain of about 20 N / cm. Thus, any textile does not need to be stronger than this. Considering the low forces of the surgeon to place a sling or a mesh, the necessary strength probably is in the range of 2 to 10 N /cm with variations depending on the degree of prolapse and the patient and her anatomy. However, more precise measurements or estimations are still lacking.

In our own investigations, we measured the tension within a suture loop and found only a moderate tensile strength of 2-3 N, which, furthermore, rapidly decreased within 1 hour to less

than 1 N by cutting through the tissue being influenced by the content of collagen within the tissue. [45] This confirms our conviction that the forces for tissue approximation are rather low.

By not properly studying a more precise strength requirement for pelvic mesh vis-à-vis the in vivo forces exerted on the mesh in the pelvis, Ethicon risked "over-engineering" or improperly engineering their pelvic mesh in much the same way they did their hernia mesh. As was seen by the Holste article and our own studies, this risk of over-engineering became reality with Prolift.

As mentioned in this report, during the development of Project Thunder, it was noted by the design team that as of 2008, pelvic floor material was still over-engineered. "There is no patient-centric PF material!...we need less foreign body material and materials that correlate to measured female pelvic physiological characteristics" [46] In their Thunder documents, Ethicon lists the maximum intravaginal pressures for selected activities. The absolute intravaginal pressure is stated at 132cm H_2O. The maximum burst pressure of meshes were listed as 163cm H_2O (PVDF), 875 cm H_2O (UltraPro), and 950 cm H_2O (Gynemesh PS).

Based on Ethicon's own internal studies, despite their recognition that complications arose from hernia meshes which were "over-engineered", by failing to address these same concerns with their pelvic meshes, they became victims of their own failures. This fact was clearly stated by Ethicon's researchers when developing Project Thunder when they admitted that their own "pelvic floor materials are still over-engineered." [47,41] This would include the mesh in the Prolift.

Interestingly, despite the fact that their pelvic floor meshes were "over-engineered", they simultaneously admitted that "We have no idea what pelvic floor pressures are…if we needed to test then the issue lies…for PFR [Pelvic Floor Repair] what pressures do we test our pressures to?" [48] This is a very revealing admission.

ii. Elasticity

Whereas elasticity in the groin was estimated at about 10% and for the abdominal wall, about 20-30%, this should be far less when reinforcing ligaments in the pelvic region. Investigations from Cosson (2004)[49] and Gabriel (2011) [50]indicate an elasticity of < 10% for fascial tissue and 15 >100% for vaginal tissue (depending on whether fresh tissue or cadaveric tissue is used). Correspondingly, elasticity for slings considered as artificial ligament should be restricted to less than 10%, whereas flat mesh, with extended contact area to elastic tissue, should provide an elasticity of more than 15%. However, as for the physiological demands in the pelvic region with regard to the range of elasticity, there is a paucity of data in the scientific literature.

Further, any structure that has to compensate tearing forces should provide only limited elasticity, as assumed for the slings or arms of composite devices. In the central flat mesh area, the strain is compensated by a larger area, and thus, should result in less strain per cm^2 than in the arms/slings. Correspondingly, the material can be reduced in these meshes. Whether the central flat mesh area should provide more elasticity than the arms by adaptation to the high elasticity of the surrounding tissues or whether it should have limited elasticity to reduce the elasticity of the prolapsed tissue is still open for debate. With the first assumption, there may be less shear stress but more mobility within the mesh area, thereby increasing the risk of cell

damage and migration/erosion. With the latter assumption, there may be less stress within the mesh area but more shear stress at the interface, thereby increasing the risk of cell damage and migration/erosion.

As stated in their Gynemesh PS "White Paper", Ethicon knew the importance of a pelvic mesh that was stretchable in all directions due to the complex, dynamic, multi-axial, three-dimensional nature of the pelvic region. "Designing a mesh …. First, it is important to consider rigidity / flexibility … [this is] extremely important when considering the dynamic nature of the tissues surrounding the vagina wall. An ideal mesh would be multi-directionally stretchable, easily conforming to tissues in the region of the repair. This would reduce the amount of tension on the fixation sutures allowing the tissue to function normally." [7]

Although on the one hand, Ethicon claims that the Prolift met the physiologic demands of pelvic tissue with appropriate strength and elasticity, its lengthy, internal biomechanical analysis stated otherwise. In what was perhaps the most straightforward presentation of the problems facing Ethicon in designing a safe surgical mesh for PFR, Juergen Trzewik and Chris Vailhe prepared a report just last year which addressed, among many other things, this problem regarding the required strength and elasticity of pelvic meshes. Their report stated as follows:

> Most of the information dealing with the biomechanical behavior of the soft tissues involved in the pelvic static [sic] are presented in the literature with very few information on the material compliance. Most of the mechanical results as presented are dealing with the mechanical behavior of the vagina and there is a very large disparity...noticed among the presented results even intra-individual results. Almost no information dealing with the mechanical behavior of the other involved tissues (rectum, bladder, uterus, ligaments, and muscles) are available. Furthermore, only qualitative information is available on the nature of the contact between organs. To illustrate the information available in the literature, one may cite Ettema et al. (1998), Goh (2003) or Cosson et al. (2004) for vagina tissue studies or Cosson et al. (2003) or Boulanger et al., (2005) for ligaments study. The proposed result is interesting for a better understanding of POP phenomenon. However, such works are difficult to be used for mechanical and numerical modelling since the specified data is only describing the tensile strength of the various tissue structures, but not the, from a physiological standpoint, more interesting stress-strain or force-elongation behavior." [29]

Bi-directional Elasticity

Ethicon received 510(k) clearance for Prolene Soft on May 23, 2000. In the 510(k), Ethicon states that "Prolene Soft Mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling. The bi-directional elastic property allows adaptation to various stresses encountered in the body." After clearance for Prolene Soft, Ethicon used the "bi-directional elasticity" language in its IFU. In 2002, when FDA cleared Gynemesh PS, the same language appeared in its IFU. In July 2007, seven years after Prolene Soft was cleared for marketing, the FDA learned that Ethicon had been selling Prolift kits for two and a half years without proper clearance. In response to Ethicon's subsequent submissions to FDA in an effort to obtain 510(k) clearance to market both Prolift and Prolift +M, the FDA

reviewer, Dr. Jiyoung Dang, questioned a number of Ethicon's claims including its claims of bi-directional elasticity and that this property allows adaptation to various stresses encountered in the body. In the August 29, 2007 email from Dr. Dang to Bryan Lisa, head of Regulatory Affairs at Ethicon, Dr. Dang states,

> You have not provided sufficient evidence to support the statement 'bi-directional elastic property allows adaptation to various stresses encountered in the body.' Although you have shown that bi-axial anisotropy exists in the tensile properties of your mesh that is dependent on the direction of knitting machine axis, it is unlikely that this anisotropic mechanical property will be able to accommodate for physiological stresses encountered in a multi-axial anisotropic environment within the body. You have also not demonstrated that your mesh is elastic. Please either remove this statement from your Instructions for Use or provide in vivo experimental evidence that your mesh has elastic properties that allows adaptation to physiological stresses. [52]

After being questioned by the FDA reviewer, various Ethicon employees attempted to find any evidence they had to support these claims. Dr. Christophe Walther (Ethicon Germany) questioned what was meant by "bi-directional elastic properties" or "allows adaptation to physiological stresses" and asked who was responsible for these statements. Vincenza Zaddem (Ethicon Engineer and Team Leader of Prolift +M) stated "the team felt justified to use the statement 'bi-directional elasticity and that this property allows adaptation to various stresses encountered in the body' because this is the same statement used in the IFUs for PROLENE Soft Mesh and GYNEMESH PS. Since this is standard data collected for meshes, **without verifying we assumed we had data for UP demonstrating it is elastic in both directions."** (Emphasis added) [53] Apparently, Ethicon also "assumed" they had this date for the Prolift.

After searching, Ethicon employees were unable to find data to support their claims and thus, they informed FDA that they would not make this claim in the IFU for the Prolift.

Elizabeth Vailhe was asked in deposition why the claim of "bi-directional elastic property allows adaptation to various stresses encountered in the body" was removed from the IFU (Page she stated: "I don't know. I provided to them benchtop data to show that the mesh had bidirectional elasticity from a benchtop, so I'm not sure what data they had about stresses encountered in the body. I wasn't asked to provide that." "The testing that we did, did show from the stress-strain curves that there was bidirectional elasticity, yes." Evidently, the FDA did not agree, and nor do I. Mesh with elasticity in two directions does not account for the anisotropic behavior of pelvic tissues or the biomechanics of the pelvis, in general. Ethicon's claim of "bi-directional elasticity" begs the questions: "Why is it important to have elasticity in two directions and not all directions?"; "How much elasticity is there in each direction, and why is that important?"; "Is the same amount of elasticity required in the arms as in the central portion of the mesh?"; "If so, how much, and if not, why not?"; etc., etc., etc. [54] Only by understanding what questions to ask, and answering those questions, could one attempt to design a pelvic floor mesh that will adapt to the stresses, and this has not occurred.

iii. Structural Stability with regard to Strength and Elasticity

Whereas for meshes placed in the abdominal wall the principle of "tension free" might be somewhat true as mentioned in the section above, the textile structures in the pelvic floor necessarily, and by definition, cannot be "tension free". Their fixation to ligaments indicates that their function has to consider resistance against tearing stress and to prevent prolapse of the tissue under mechanical strain. Thus, any claim by Ethicon that their pelvic meshes are "tension free" is false and misleading.

Due to the anisotropic behavior of warp knitted meshes, their characterization by uniaxial testing is insufficient to reflect stability and elasticity. At uniaxial strain, right-angled to the course of the warp fibres, these anisotropic meshes show marked elongation and narrowing in width. In slings, the stretching favors enrollment and in meshes it may favor folding, which both lead to local accumulation of material and enhancement of inflammation and fibrosis. Correspondingly, textiles subject to tensile strength should provide a higher structural stability to maintain a flat and stable geometry, even under strain. Elongation of a knitted PP textile results from deformation of pores, and as the elongation is increased, leads to further narrowing of the pore diameter, thereby reducing the area of sufficiently large pores. This occurs with Prolift and is a significant deficiency. Correspondingly, textiles subjected to tension should provide a higher structural stability to maintain large pores, even under strain.

Elasticity testing with a stamp/plunger reflects the two-dimensional strain better. Tensile strength as N/cm can be calculated as outlined in US Patent No. 6,162,962 Dec 19, 2000 from Ethicon. [55] However, such testing does not reflect the specific configuration of stress compensation within the two-dimensional structure; in particular it does not reflect the change of pore geometry. Furthermore, stretchability of the material is blocked by circular fixation of the mesh in the frame of the testing device; thus, comparison with uniaxial elasticity is limited.

However, in general and unfortunately, the huge variety of the different tests (different settings for measuring stability, elasticity, or porosity) that are applied by mesh manufacturers, hinders the direct comparison of the material properties.

The elasticity is markedly less for Gynemesh PS Mesh®. During the manufacturing process the mesh used in the Prolift kit is laser cut off of a large piece of Gynemesh PS, the edges of the Prolift mesh are still frayed leaving the end of the filaments "barbed" with irregular, sharp edges. At very low strain, the Prolift arms show a considerable rolling in, sometimes referred to in Ethicon documents as "mesh curling", "roping", or "lack of stress-shielding".

Furthermore, due to the different course of the filaments within the arms, there are marked differences in its elastic behavior and the deformation of the pores under strain, when comparing the posterior arms with the anterior arms. Notably, even after relaxation of the arms after strain, the "curling" of the arms persists indicating a plastic deformation of the structure. The failure of the structure to return to its original or near original shape is known as "lack of memory".

The frayed edges, "roping" and "curling" under minimal strain, excessive elasticity leading to pore deformation under strain, and lack of memory after strain, all are design failures

that cause Prolift to have an unsafe design that unreasonably increases the risk of injury to patients in whom it is implanted. [Fig. 5]

c. Biocompatibility

Although one of the initial considerations of prosthetic mesh design construction by medical device manufacturers should be the biomechanical requirements, the second important consideration should be biocompatibility. Biocompatibility of long-term implantable medical devices can be defined as the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host. More simply put, biocompatibility entails optimal cellular response and tissue ingrowth. Piet Hinoul, medical director agrees in his deposition that it was important for Ethicon to develop a mesh construction that would ensure only the desire amount of fibrosis would occur and also that "you would want to limit excessive fibrosis. [54a]

The intended function of biomaterials for hernia repair is reinforcement of the abdominal wall inducing scar tissue. Since Usher's introduction of biomaterials into hernia surgery in 1958, our understanding of mesh biocompatibility has been continuously developed. Histopathological investigations have shown that the amount of fibrosis is directly related to the amount of the inflammatory, cellular foreign body reaction (FBR) induced at the biomaterial/host-tissue interface. We thus decreased the surface area of the mesh materials in relation to the physiological biomechanical requirement to minimize the biomaterial/host-tissue interface area. This realization and design shift led to our development of what became known as "the lightweight, large pore concept" as detailed earlier in this report. Although this concept met with measurable resistance in the early days, the superiority of lightweight, large pore meshes over the classical heavyweight, small pore mesh materials is now widely accepted. These large pore or "macroporous" meshes, defined as pore sizes of >1mm in all directions, have a decreased surface area, and compared to classical mesh materials, they induce a reduced inflammatory reaction with a decreased amount of clinical complications.

i. Porosity Storyline

In the late 1990's, as we were developing the lightweight, large pore concept, we had no way to measure the pore sizes in an objective, reproducible manner. We concluded from our work with Ethicon in developing Vypro and our published results from comparison studies in animals in 1998 and with explanted meshes from humans in 1999 that improved biocompatibility of meshes could be achieved by using a mesh design that was adapted to the previously-undefined physiologic requirements of the host tissue (pressure, strength and forces) with less alloplastic material and an optimized structure (more elasticity and larger pores) while at the same time, maintaining sufficient tensile strength. Our studies also showed that Vypro accounted for less inflammatory response and less mesh contraction or "shrinkage" (34% vs. 46%). The design characteristics of Vypro that accounted for this improved biocompatibility included a weight of 25 g/m^2 (<30% of the weight of Prolene), 20% elasticity at 16 N/cm, and pore size > 3-5mm (pre- and post-absorption of the Vicryl fibers). For these reasons, we felt at that time that we had achieved a more optimal, biocompatible surgical mesh design with Vypro. Other researchers at the time agreed [19]

In the months and years following our publications regarding these new concepts, a few things of note occurred: First, manufacturers rushed to develop and market "lightweight" surgical meshes using marketing language like "soft", "supple", "easier to handle", "more flexible", etc. Their focus became somewhat myopic with perhaps too much emphasis being placed on the weight of the material. To some extent, these manufacturers, including Ethicon, became trapped in their own marketing slogans.

Second, in light of continuing patient complaints and complications related to surgical meshes, and with various conclusions being put forth with regard to the new lightweight/large pore concept, there was a "vigorous search for new meshes with better biocompatibility." [56]

ii. Classification

As further research was conducted and the medical and scientific communities moved forward and looked more closely at design considerations and their effect on complications, certain studies demonstrated that biocompatibility was enhanced more from larger pore size than material reduction. Weyhe et al. did a comparison study of heavyweight versus lightweight meshes to evaluate whether weight and structure of PP meshes were independent determinant factors for tissue incorporation of the implant. Their conclusion was that there can be worse biocompatibility of lightweight meshes compared with heavyweight meshes, if the lightweight fleece has very small pores. "Thus, the amount of implanted mesh was not the main independent determinant of biocompatibility (expressed as successful incorporation and diminished foreign-body reaction) but the size of the pores." [56] As between "lightweight" or "large pore", large pore was considered by far as the most important design construct for maximum biocompatibility and thus a potential deterrent to mesh-related complications.

Not surprisingly, attempts to objectify the weight parameters or values for the best "lightweight" design were inconclusive and/or varied. A review of the scientific literature indicates that there has been no real consensus as to the categorization or definition of the weight limits by class:

- Cobb (2004) lists Marlex as a "heavyweight" mesh at 95 g/m^2; Prolene Soft as a "midweight" at 45 g/m^2; and Ultrapro as a "lightweight" at 28 g/m^2; [19]
- Cobb (2006) states that "lightweight meshes tend to have 35 g/m^2 of PP or less; [57]
- Weyhe (2008) defines "lightweight" as 35 g/m^2 and a "heavyweight" as 95 g/m^2; [58]
- Deeken (2010) defines "ultra light-weight" as less than 35g/m^2, "light-weight" as 35-50g/m^2, "medium-weight" as 50-90 g/m^2 and "heavy-weight" as >90g/m^2. [59]

Ethicon's documents reveal varying values for the weight of its PS mesh from 42.7 g/m^2 – 45 g/m^2. [60,61,62] In numerous documents in which they communicated their mesh weight classification to FDA, surgeons and patients, Ethicon stated that Prolene Soft/Gynemesh PS/Prolift were "lightweight". However, according to Cobb and Weyhe, at least, Ethicon's PS

mesh was "mediumweight", whereas Vypro, Ultrapro and Prolift+M would be considered "lightweight". The deposition testimony of a key Ethicon employee also reveals Ethicon's lack of understanding as to what constitutes "lightweight". In 2008, Vince Lucente, a urogynecologist who was the number 1 promoter of Prolift and Prolift +M, referred to Gynemesh as a "middle weight mesh". (62a)

Ethicon Worldwide Medical Director, Piet Hinoul gave testimony regarding the difference in fiber and/or overall weight of Ethicon's surgical PP meshes. Although it is well known and documented that Prolene Soft Mesh/Gynemesh PS was designed to be the "lightweight" version of its Prolene Hernia Mesh in an attempt to reduce complications, Ethicon Medical Affairs evidently does not know the difference between the meshes. In fact, in the second day of Piet Hinoul's deposition testimony, he stated that he does not know whether complications would be reduced by using Prolene Soft Mesh/Gynemesh PS versus traditional Prolene mesh "...I do know that both of them are lightweight meshes. So, with that respect, there will be a lot of similarity..." [63]

Notwithstanding this question of whether Prolift is considered to be a "lightweight" mesh, as mentioned above, weight is not nearly as important as porosity. As one author put it:

The weight of the mesh depends on both the weight of the polymer (*specific gravity*) and the amount of the material used. Heavy-weight meshes usually have small pore sizes, whereas light-weight meshes are constructed with large pores. However, keeping in mind that different polymers have different specific gravities (PP = 0.9 g/cm^3, PVDF = 1.7 g/cm^3), and not all light-weight meshes are constructed with large pores, **this classification is meaningless.**" (emphasis added) [64]

Recently, in the journal *Hernia*, Coda et al. proposed a system involving the grouping of simple, composite or combined meshes, based on defining the weight as follows [65]:

1. Ultralight ≤ 35 g/m^2;
2. Light C 35-70 g/m^2;
3. Standard C 70-140 g/m^2;
4. Heavy C ≥ 140 g/m^2.

However, there appears to be no rational explanation for these weight borders. Though lightweight usually indicates reduced material, it does not differentiate between film, fleece or net-like structures. Despite the fact that new polymers are on the market with high specific weight resulting in heavyweight meshes, their big pore size results in excellent biocompatibility. Other meshes are constructed as composites providing special features, which also cannot be defined by a simple weight category.

Furthermore, any characterization of meshes by their biocompatibility, stability or elasticity, which should be a primary consideration given that these characteristics are related to the task of meshes in reinforcing the host tissue, is limited by the fact that most of the meshes show a marked anisotropy. This hinders the application of all uniaxial tests and makes reliable comparisons impossible and correspondingly, hinders its use for classifying mesh devices.

Therefore, to try to overcome some of these inconsistencies and hurdles, and to try to provide valuable guidance to surgeons who are considering whether to implant a mesh and if so, which ones, we set out to create a new classification of hernia meshes. Rather than using weight as the defining parameter, we contacted major manufacturers of meshes in Germany and collected their physicochemical data of their products with the goal of deriving a classification system that grouped meshes according to their biocompatibility.

First, it is important to look at the "old" Amid classification system to understand the context for his first classification. [66] He presented his first attempt at classifying hernia meshes in 1997. His study was focused on the risk for infection in hernia meshes and separated them into 4 classes:

ii) meshes with "large pores"
iii) meshes with "small pores" < 75 µm
iv) combination of 1 and 2
v) films with submicronic pores < 10 µm

Amid's classification of hernia meshes did not focus on biocompatibility or foreign body reaction, nor did he include meshes with large pores of >1 mm as meshes with pores of this size (Vypro being the first) had just entered the market in Europe. Also, this analyzed meshes for use in the abdomen, not the pelvis. Given that shortly after Amid's classification was published there were newer, larger pore meshes on the market, his classification actually needed some revisions not long after it was published to more accurately account for the newly-published data regarding 1mm pore size and its relation to biocompatibility.

Considering the huge changes that have taken place in the mesh industry since Amid's classification, and with input from all of the major surgical mesh manufacturers in Germany and a review of approximately 1,000 explanted mesh samples, my colleagues and I prepared a modified hernia mesh classification:

1. large pore: textile porosity > 60%, effective porosity > 0%
2. small pore: textile porosity < 60%, effective porosity = 0%
3. meshes with special features (added barrier, bioactive coating etc)
4. meshes without pores (films or film like)
5. 3D devices, without clear physico-chemical characterization
6. biologicals (synthetic absorbable, non-synthetic absorbable or non-absorbable)

As we stated in our published article, it is important to note that even if a hernia mesh is considered "large pore" based upon the above classification, in order to avoid "fibrotic bridging" (discussed below), even large pore meshes must have a sufficient amount of "good pores" (> 1mm) in order to resist this consequence of the inflammatory process.

This classification will be used for the quality assessment of hernia meshes in order to help surgeons and manufacturers determine whether the mesh itself meets the minimal critical to perform adequately, or whether the indication is appropriate. Any significant deviation that is

noted from the risk profile in comparison to other members of the same class will then lead to further analysis as to whether a product is appropriately classified. [67]

iii. Foreign Body Reaction (FBR)

Our work in developing Vypro with Ethicon and our published studies thereafter led us to the conclusion that porosity is a decisive design characteristic for proper tissue integration. It is a widely-known fact that all experimental and clinical studies indicate that all mesh products on the market today cause an initial and chronic inflammatory tissue response in the recipient after implantation. The quality of the inflammatory reaction to foreign bodies of different natures is surprisingly constant, characterized by a rapid accumulation of huge numbers of phagocytic cells, in particular, blood monocytes and tissue-derived macrophages. This type of inflammatory process is known as a foreign body reaction (FBR).

The FBR is characterized by an initial inflammatory burst caused by a release of a huge cocktail of potent inflammatory mediators which then attract other cell types including T-cells, polymorphonuclear granulocytes (PMNs), plasma cells and fibrocytes. Within a few days, this cellular activity forms an early granuloma layer recognized by the very typical foreign body giant cells and an outer layer of fibrosis with deposition of collagen. This late stage granuloma is not a static type of chronic inflammation but rather, it represents a chronic wound with an increased cell turnover even years after implantation. Monocytes and tissue-derived macrophages, at the interface and in contact with the polymer, undergo apoptotic cell death and are replaced. [Fig. 6]

We published our results in 1998 and 1999 of the histological analyses from explanted mesh from rats, dogs and humans. The tissue response in humans was almost identical to the morphological observations in the animal models. In our 1999 study, we reviewed approximately 350 human explant samples of various mesh modifications gathered from centers all over Europe. Even 15 years after explantation, the longest observation in our study, a persistent chronic FBR could still be detected, indicating that mesh is likely never completely inert with respect to local inflammatory processes. The persistence of this FBR is important, especially in younger patients in whom the mesh will remain for several decades. The delay before explantation of mesh for infection of up to 56 months, for chronic pain of up to 48 months and for recurrence of up to 180 months established that in many clinical studies with shorter surveys of less than 1-2 years, the morbidity rates are underestimated. [68, 69, 70]

iv. Fibrotic Bridging

In our studies from the late 1990's, in which we evaluated the inflammatory response in the tissues at the interface with the mesh implant, we saw that that large pore mesh (Vypro) was integrated into a loose network of perifilamentous fibrosis with fat tissue present in between the fibers. In contrast, the small pore mesh was incorporated entirely in perifilamentary granulomas and scar tissue, which bridged the whole pore diameter <1 mm. This phenomenon, known as "fibrotic bridging" exists when granulomas, side by side, form a common outer fibrotic capsule joining each mesh fiber and forming a rigid "scar plate' covering the whole mesh. This scar plate leaves no space for further tissue ingrowth and leads to a number of complications

including loss of elasticity and pain associated with the rigidity, shrinkage or contraction of the mesh, mesh erosion, nerve entrapment, bacterial encasement, chronic pain and dyspareunia if used in pelvic floor repair.

With the development of Vypro, the first truly large pore mesh, we were able to increase the pore size by up to 500-600% (Vypro 3-5 mm vs. Prolene <1mm). Given that the risk of bridging fibrosis is increased by mesh with pore size < 1mm in all directions, any mesh designed with pores this small increases the risk of injury to the patient and is a less safe design than mesh with pore sizes > 1mm in all directions. Simply put: the greater the pore size or open space in between fibers, the less the risk of fibrotic bridging and formation of a rigid and potentially dangerous scar plate encapsulating the mesh. Ethicon had this information beginning in 1998.

v. Effective Porosity

In approximately 2005, I applied for and received a grant to study the porosity of textile meshes in an attempt to objectify porosity in a reproducible manner. I contacted an engineer at the FH Aachen University of Applied Sciences, Thomas Muhl, and we embarked on a two-year project to create a novel and unprecedented porosity image analysis system. The results of this granted project were published in 2007 in the *Journal of Biomedical Materials Research Part B: Applied Biomaterials.* [71]

In working with Prof. Muhl, I shared with him some of the findings from over 10 years of research. I informed him that because the inflammatory and fibrotic intensity of a foreign body reaction largely depends on the porosity of the implanted material, the pore size as well as the pore geometry will define the capability of the device to allow tissue ingrowth.

Prior to this research, scientists had been using bicolor images to analyze porosity by adding all of the lighted pore areas in the sample and dividing that number by the total area of the sample. This equation provided a two-dimensional porosity of the mesh sample, including *all* pores, regardless of their size and geometric shape.

Through our work, we wanted to have a better understanding of what happens to porosity in vivo with regard to the FBR and the body's normal physiological stresses. From my prior work, we knew that pore sizes that prevent fibrotic bridging and will permit tissue ingrowth should exceed 1 mm between two PP filaments. As stated in our publication, "To exclude large pore areas that may be provided by long and thin pores with narrow parts of pores, the pore geometry has to be evaluated as well. Therefore, only those pores and those parts of the pores are extracted, which have dimensions greater than 1000 µm in all directions. The remaining porosity is defined as 'effective porosity'".

If effective porosity would tell us more about the resulting pore geometry after accounting for the granulomous effect of the estimated FBR, then putting the mesh sample under various amounts of force would give us some good and useful data regarding how the pore geometry would be affected under the physiologic strain of dynamic anatomic structures. Because of the high stiffness of the individual polymer fibers, the elasticity of textile implants usually results from a deformation of the pores, leading to a marked reduction of the effective

porosity once mechanical stresses are applied. Thus, we measured the "effective porosity under strain" of certain mesh test samples in our study to determine the product's structural stability. [Fig. 7]

Furthermore, because having only a small percentage of large effective pores, either in one area of the mesh or across various areas of the mesh, would not be sufficient to protect against bridging fibrosis, we developed software that would report a "histogram" of pore size. The histogram provides information about the distribution of effective pores throughout the mesh sample. The right axis of the histogram gives the porosity calculated as a ratio of summarized pore area/total area. [Fig. 8]

vi. Testing of Ethicon's Surgical Mesh Products - Effective Porosity under Strain

In connection with this litigation, Prof. Muhl performed testing on various Ethicon surgical mesh products (as well as on a PVDF mesh with a different structure from FEG, Aachen) using the same protocol as we used in our study in 2007. (NOTE: An Ethicon R&D Scientist, Vincenza Zaddem, Team Leader of Prolift +M and Technical Lead of Prolift, was shown the Muhl study from 2007 and she testified that it sounded like a valid test and that she believed that it would be a good test for Ethicon to look into in order to determine the effective porosity and effective porosity under strain of their pelvic meshes. [72]

Based upon the findings in his report, I have the following observations [73]:

Prolene Soft Mesh (Gynemesh PS/Prolift)

The textile porosity of Gynemesh PS (PS) is 63% higher than Prolene. The effective porosity of PS is about 26%, but in the arms the porosity decreased rapidly under strain, dropping to 0% at a strain of 5 N. These numbers reflect a considerable percentage of pores smaller than 1000 µm in diameter in all directions and considerable loss of structural stability when subjected to minimal force.

Under 4.9 N/cm of strain, Prolift reaches an elongation of 15% in the warp direction and 22% in the cross direction. The textile porosity decreased to 50% at a strain of 4.9 N/cm if the strain was applied perpendicular to the warp course or to 57% if the strain was applied in line with the warp fibers. Any large "effective" pores completely disappeared at a load of 4.9 N/cm if the structure was stressed right angled to the warp fibres. In comparison with the center, the arms showed different behavior under strain.

For the three arms, elongation at 4.9 N/cm was even higher and reached 22%, 25% and 27%, respectively. Textile porosity was reduced more as well to 41% and 37% for Arm 1 and Arm 2, respectively, and was even decreased to 10% for Arm 3. Any effective porosity disappeared at a strain of 4.9 N/cm in Arm 1 and Arm 2, and disappeared at a lower strain of 2.5 N/cm in Arm 3.

Overall, there was only slight anisotropy in the center flat mesh with an elongation of 20% at low mechanical burden. Effective porosity disappeared at a load of 4.9 N/cm. These characteristics were widely maintained in the structure of the arms, though effective porosity in Arm 3 disappeared at the lower load.

Dynamesh- (PVDF from FEG-Aachen, Germany)

The textile porosity of the center of Dynamesh, made of PVDF, which incites a less intense FBR than PP, and thus requires lower effective porosity to prevent bridging fibrosis, was 63.3+/- 0.6 %, whereas the effective porosity was 56.5 +/-1.2 %. The minimal difference between textile and effective porosity reflected the fact that most pores had a diameter of larger than 600 µm (the minimum distance between filaments to calculate effective pore areas, and thus the effective porosity, of PP is 1000 µm and 600 µm for PVDF). The elongation was more when tension was applied in the cross direction (9% at 4.9 N/cm) vs. the warp direction (4% at 4.9 N/cm). At a strain of 4.9 N/cm in the cross direction, the textile porosity decreased only slightly to 62.7%. The effective porosity at that strain decreased only to 54.7%. In the warp direction the textile porosity decreased to 59.9% at 4.9 N/cm and the effective porosity to 52.5%.

Dynamesh has a symmetrical shape. The arms are oriented in the same direction in reference to the mesh structure. Therefore, only one arm (Arm 1) was measured and taken as representative for all four arms. At 4.9 N/cm of force, the arm maintained 60.8% textile porosity and 54.6% effective porosity.

Overall, the textile showed remarkable effective porosity and high effective porosity persisting even under strain whether the measurements were taken in the center portion of the prosthetic or in the arm. It also showed roughly equivalent performance under strain whether being tensed in the warp or cross direction. In sum, Dynamesh (PVDF) showed excellent structural stability under tension and excellent effective porosity to resist fibrotic bridging. Another significant observation of the Dynamesh product is that unlike Prolift, Dynamesh has a smooth seam around the entirety of the mesh with no fraying at the edges nor curling in the arms under strain as was seen with both of the Ethicon products.

vii. Structural stability – Deformation of Pores/Curling/Fraying

The significance of the Muhl method of testing these mesh products is that it provides useful data in terms of how the mesh, and different parts of the mesh, will perform in the human body. The first most important observation from this testing was that the effective porosity and the effective porosity under strain in Prolift produced less than optimal results. As minimal strain was applied to the test sample, the geometric shape of the pores deformed and ultimately collapsed. This deformation led to extremely small pores which would make the mesh highly susceptible to fibrotic bridging, encapsulation by a rigid scar plate and the array of potential complications that occur as a result of this inflammatory process.

Ethicon has indicated in its internal documents that a force of 12.0 lbf (53 N) is placed on the mesh arms of the Prolift during implantation and that the required forces to pull the mesh arms through the cannula to be 0.73 lbf (3.24 N). [74,75] It has also stated in other documents that the tensile strength of the implant straps “shall exceed 2.3 kg-force” (23 N) [76]It is also axiomatic, as stated more fully earlier in this report, that pelvic floor repair in the anterior or posterior chamber cannot be a “tension-free” repair. While attached to the pelvic floor ligaments and while imbedded in pelvic tissue that will be subjected to years of stress loading and stretching of the pelvic floor tissues, Prolift mesh will be subjected to dynamic, three-dimensional, multi-axial forces on a daily basis in the life of any of these women in whom the

device is implanted and certainly more force than was applied by Prof. Muhl during his testing of these meshes.

As a result of the known forces that will be placed on the center portion of the mesh as well as the arms, coupled with the observations and testing by Prof. Muhl on the Prolift lacks the sufficient structural stability to perform safely in the human body with regard to effective porosity and effective porosity under strain.

Another significant observation during the porosity testing by Prof. Muhl was the "curling", sometimes referred to as "roping", that occurred in the mesh arms of the Prolift under minimal strain. We published an article in 2007 [77] in which we showed the tissue reaction and fibrotic ingrowth of PP due to curling/roping of the mesh due to scar shrinkage after H&E staining. [Fig. 9] As strips of mesh begin to curl, they act similarly to small pore meshes in that the fibers become situated too close together enhancing the inflammatory response and leading to fibrotic bridging.

Regarding curling, in the December 2000 Corporate Product Characterization monthly report, there was a discussion of the development of a line extension of Prolene mesh to Prolene Soft mesh. During the design verification activities, a protocol was executed for mesh curling. Ethicon defined mesh curling as "the retention of a non-planar shape after applying and removing a force in any direction of the material." Their test parameters were determined by using a PP mesh "known for its 'bad' curling quality". They applied a force to a strip of mesh and the behavior of the material was observed after the removal of the force. Ethicon claimed that the Prolene Soft "did not remain curled after the application and removal of a two-pound force." [78]

From this document, it is unclear as to the chosen width and length of the strips of mesh that were tested. However, assuming they were testing a mesh strip sample that was roughly equivalent to the Prolift arms, their test results would be vastly different from the results noted above from Prof. Muhl's testing. With just a load of 3 lb/in in the Muhl testing, the arms from the Prolift sample, curled, deformed, and did not return to their original shape.

Yet another significant observation during the porosity testing by Prof. Muhl was the "fraying" at the edges of mesh which could be seen upon removal from the package but became markedly worse in the Prolift mesh sample at minimal strain. These frayed edges act like "barbed-wire" in the pelvic tissue creating an increased inflammatory process. When frayed edges occur in the curled arms, an even greater inflammatory process is created.

After being subjected to even minimal strain or tension, the arms in the Prolift not only curled, frayed and demonstrated deformation of the pores, they also failed to return to their original or near-original geometric shape and design. This phenomenon is known in material science as plastic deformation and is sometimes referred to as a lack of memory.

From the internal documents as well as the sworn testimony of high-ranking Ethicon employees, it is readily apparent that there was a fundamental lack of understanding of the design requirements of pelvic meshes, the body's reaction to these meshes and the complications that are related to the design construct and the host defense response. This was especially true

for their proper understanding of "tension-free" mesh in the pelvis for reinforcement of pelvic organs as well as the cause and consequences of mesh "curling" or "roping".

For example, Dr. Piet Hinoul, Ethicon's Worldwide Medical Director testified that: "...we advocate a tension-free placement of the mesh and the support and the suspension is generated by the arms and the way it's pulled through the tissues and ligaments. Additionally, Dr. Hinoul testified as to the question of tension on mesh changing the pore size, that: "and this is probably what you were alluding to earlier about effective porosity. If you have a pore that's let's say 4 millimeters if you put it under tension, then your effective pore size between these two may be 2 and this may be 6... I think this is the reason exactly why we want the mesh to be placed tension free, so the porosity remains as it is designed." [79]

Dr. David Robinson, Ethicon Medical Director prior to Hinoul, seems to have some confusion as to how to place a Prolift in a "tension-free" manner. When asked at his deposition about the surgical guide technique guide referring to "tension free", whether that means there should not be tension on the mesh arms or the mesh body, he testifies: "Well, they'd have to -- I guess it goes to what tension means, but, I mean, they have to have some resistance to displacement. That's different than tensioning them. I'm not sure." When asked: "...is there any statement in this surgical technique that gives a physician some measure to understand whether or not they've achieved tension free so that they'll know what they're trying to achieve, some objective measure?" He responded: "No. We had no tool to objectively measure tension. It was not something that's taught probably at the preceptor or proctor level as well as on cadavers as to what that would mean." [80]

Evidently, there were actually Ethicon employees who understood the unfounded nature of claiming that pelvic floor meshes could somehow be "tension-free". In the Trzewik/Vailhe biomechanics report, under "guidelines for implant design", they state that in order to "adopt physiological constraints to develop reasonable requirements" for proper biomechanical design of pelvic meshes, Ethicon had to consider two types of loading or tension on the mesh in vivo: "constant, static load = 2.5 kPa (caused by organ weight)" and "dynamics load = 10-20 kPa (caused by one-time actions like coughing)". Clearly, Prolift is subjected to pressures in vivo, which would ultimately lead to tension on the mesh both during implantation and in vivo. Ethicon's statements that its pelvic floor meshes were "tension-free" were false and misleading. [29]

Dr. David Robinson also testified [81] that "roping" is used to describe the act of pulling on a mesh hard enough to exceed physiological tension causing it to "rope out". He states that Ethicon did testing to establish how much force would cause this to occur with a TVT sling, and as to Prolift "It's the same mesh, so it would operate in the same fashion."

Scott Ciarrocca, Ethicon's Associate Director of R&D, testified at his deposition [82] that he is not aware of an objective definition of "tension free"; he is not aware of complications being caused by too much tension being placed on the mesh; and tension to the mesh was not discussed during design process.

While developing the Ethicon Project Thunder mesh (PVDF), the R&D team actually considered the relationship between tension or "over-stretching" of the mesh and pore collapse or "deformation". Ethicon referred to this design principle as "stress shielding". [83,46] In two

separate PowerPoint presentations by the Thunder team, there is not only a discussion of the need for their mesh to have "stress shielding...to avoid pore-collapse, deformation and pre-stretch", they also include macroscopic and microscopic photo analysis of their mesh showing reduced pore size due to collapsed pores under a uniaxial load of merely 1N. [Fig. 10]

Images of pore collapse and deformation under stretch were depicted again in an Ethicon biomechanics PowerPoint. This extensive presentation highlighted the challenges in designing a mesh implant for an area of the body (the pelvis) where no descriptive model was available to predict the mechanical behavior of the mesh. The three macroscopic images of pore deformation, mesh tearing, and edge fraying under increasing amounts of strain depicts a product that will be unsafe, vis-a-vis structural stability and biomechanical predictability. [Fig. 11]

Yet a third reference to the variability of pore size under applied load is contained within the Trzewik/Vailhe report entitled "Biomechanical Consideration of Pelvic Floor Mesh Design" reference above. As stated in that report, "Pore size is a crucial measure for the safety and efficacy of mesh implants. Whether or not an implant may be exposed to scar plate formation is determined, in part, by the obtained pore size. Figure 8 clearly illustrates the impact of an applied load to the resulting pore size. For mesh strips, even a mild loading of 1N has a dramatic impact on the resulting pores size as far as soft meshes like Ultrapro are concerned. Under this loading the initial pore size of between 3-4 mm decreases to values down to 0.3mm. [Fig.12;] [29]

In fact, in that report there are other macro- and microphotographs of attempts by Ethicon to design their pores with "stress shielding reinforcements" that were constructed using fibers "or by other elements like long time absorbable PDS-film". These design constructs, these photographs, and this discussion of the known phenomenon of pore size variations as a function of the applied load demonstrates Ethicon's knowledge of design failures and flaws of Prolift.

As stated above, unlike the Prolift, Dynamesh (FEG), a pelvic floor mesh made of PVDF, as demonstrated in the Muhl testing and in the scientific literature, has superior characteristics in terms of effective porosity, effective porosity under strain, less foreign body reaction, resistance to pore deformation, and resistance to curling. It also does not demonstrate frayed edges at its borders unlike the Prolift.

A mesh device that is permanently implanted in human tissue and reacts to in vivo conditions in the manner in which the Ethicon meshes performed during Prof. Muhl's testing increases the risk of injury to patients in which it is implanted and is a less safe design than products that better withstand these in vivo conditions and do not display these poor outcomes. The PVDF product is a safer design for all of the reasons stated above.

viii. Ethicon's Claims & Considerations re Porosity, Inflammatory Response, and FBR

Ethicon's statements as well as its claimed benefits regarding porosity, tissue ingrowth, inflammatory response, FBR, and related biomaterial science considerations in relation to patient

complaints and complications are at times inaccurate, misleading and/or false and should be questioned:

Repeatedly in Ethicon's Prolift IFU they make the following statement:

- **"Animal studies show that implantation of GYNEMESH PS mesh elicits a minimum to slight inflammatory reaction,"** - Animal studies mainly are done by testing the material in the abdominal wall without contamination and without putting mechanical strain to them. Thus, this statement should have been limited to the precise conditions of the preclinical testing. Also, in countless references in the literature it is stated that there is an *intense* host defense response immediately after implantation. As such, this statement is inaccurate and misleading and should be changed accordingly;
- **"which is transient"** – Although immediate post-operative inflammation due to the implantation may resolve within days or weeks, there is sufficient evidence that the inflammatory foreign body reaction around an implant persists for years, and thus cannot be regarded as transient. As such, this statement is misleading and should be changed accordingly;
- **"is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue."** - Large pores (>1mm in all directions) are required to prevent bridging fibrosis. At least in terms of the arms, under strain, there is a marked reduction of pore size, resulting in curling of the textile, plastic deformation of the geometry, jagged/sharp edges, which can lead to fibrotic bridging and encasement of the prosthetic in a rigid scar plate, all of which calls into question adequate biocompatibility and thus, proper tissue integration/incorporation. Thus, a restriction of this inadequate statement is necessary;
- **"The mesh remains soft and pliable"** - This is in contrast to some reports about a solid mass in the area of the implanted mesh, which is assumed to be the shrunken implant embedded into scar tissue, as has been confirmed by ultrasound. See also the statement immediately above regarding "tissue incorporation". In many patients, the mesh remains anything BUT "soft and pliable" and thus, this statement is incomplete and could be misleading;
- **"normal wound healing is not noticeably impaired."** - This statement obviously is not always true, as erosions are well known to Ethicon to occur, which are in stark contrast to "normal wound healing". Furthermore, given the intense FBR that occurs at the tissue-implant interface, the chronic inflammatory response leads to chronic wound healing issues in many patients. As such, this statement is only true in some patients whereas for many others, it is false and misleading and should be revised accordingly;
- **"The material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes."** – As mentioned earlier in this report, there is sufficient evidence for the fact that polypropylene shows degradation after incorporation in tissue, though the precise clinical relevance has been debated in the scientific literature. Certainly, numerous studies have cited instances whereby degradation occurs more frequently in the presence of infection at the wound site. Ethicon was, or should have been, aware of this literature and was certainly aware, according to its documents, of the degradation of the PP in its meshes. Thus, this statement was known by Ethicon to be false and misleading. [8, 84]

ix. Ethicon's Knowledgebase of Biocompatibility in the Pelvic Mesh Era

1. 1998-2002: Klinge/Klosterhalfen animal and explant studies following development of Vypro re requirement of 1mm pore size to prevent fibrotic bridging. In March 2002, my colleagues and I published our findings when comparing Vypro to small pore, heavy-weight Prolene mesh in a rat study. We found that the large pore mesh integrated well with plenty of fat tissue in the pores, maintaining elasticity of the implant and preventing scar tissue from bridging across the mesh. The Prolene mesh not only induced a greater foreign body reaction, but was also imbedded into the granulomas and scar tissue, bridging the whole diameter of any pores under >1 mm in diameter and not allowing for adequate tissue ingrowth. We surmised that a large pore size, perhaps 1.5 mm would allow proper fluid transport through the mesh, aiding in proper healing. This study was funded by Ethicon. [68, 69, 70, 85]

2. ~2002: Klinge/Klosterhalfen present the large pore concept to principals from J&J (US) who reject the idea of bridging fibrosis due to inadequate effective porosity under strain.

3. 02-08-2002: Gynemesh PS Design Validation Strategy: Pore size cannot be confirmed in a validation study. [86]

4. 07-03-2002: Dan Burkley porosity measurements showing less than 50% porosity on all of the Prolene meshes at that time. [87]

5. 2003 Gynemesh PS "White Paper": "Pore size is also an important characteristic. ... A pore size of 75 µm is necessary for the in-growth of blood vessels ….proper tissue integration...influenced by … infections, foreign body reactions and mesh characteristics such as rigidity , mesh density and mesh porosity...the extent of chronic inflammation in the tissues adjacent to the mesh is directly related to the amount of foreign material left in the patient. ... An ideal mesh would be as lightweight as possible without sacrificing the structural integrity needed to provide support to the native tissue". [88]

6. 04-2003: Dan Burkley email attaching his 2002 measurements and stating that this is all of the porosity data that he had accumulated on the various meshes and that he had "very little information on 'pore size'"; Earlier in that email confusing calculations regarding pore size of Ethicon meshes in square inches. [88] All pore sizes in the literature and numerous other references in Ethicon documents to pore size are all in metric values. Ethicon was confused or misguided regarding what constituted sufficiently large pores to make their products safer. They could and *should* have contacted the consultants who had worked with them for years developing Vypro (myself and Klosterhalfen), but they failed to do this until 2006, after Prolift was launched. There appeared to be a disconnect between JNJ/ETH in the States versus their European counterparts. At the very least, they could have read our articles regarding their own products to see that pores were being measured in mm and that optimal pore size to prevent fibrotic bridging was > 1mm.

7. 10-14-2003: Gene Kammerer email to "Georgina NG" which is again a confusing discussion about porosity. Kammerer states that "…the way we generally measure the pores is by the diameter or average width across the holes. This assumes a fairly consistent width of the hole." [89] As was demonstrated quite clearly from Prof. Muhl's testing, having consistent width is not the correct way to demonstrate adequate pore construction nor is measuring "average width across the holes".

8. 11-2004: First TVM published article stating that "Porosity is also a major mesh characteristic…Fibroblasts, collagen fibers and neo-vessels will be incorporated if they can circulate easily between the stitches, provide the pores are large enough. An estimated 75 µm threshold is required to obtain adequate tissue integration. In the absence of pores with an adequate size, the prosthesis will be encapsulated instead of being integrated into the surrounding tissue." It is unfortunate that these authors, who were working with Ethicon, were evidently ignorant of the work done by Ethicon and our team as well as our resultant publications in which we stressed that explanted meshes with pore size < 1mm were more susceptible to fibrotic bridging, and essentially establishing the inadequacy of the Amid classification. This is especially true because our publications predated this TVM article by 5-6 years! [90]

9. 2/28/05 DDSA re "biocompatibility" The design team did not properly assess the "Probability of Hazard" as to whether the Prolift device was biocompatible. The comment to this risk assessment merely stated "this material, when used as a suture has been reported to be non-reactive and to retain its strength indefinitely in clinical use." [91] According to this document, the Prolift design team did not perform a risk assessment for the cellular response, tissue integration, foreign body reaction, physiological adaptation or chronic wound healing characteristics of the textile mesh product. As such, their design assessment was a flawed process that endangered patients.

10. 2005: We published "LW/LP mesh concept" (cited abundantly by Ethicon in their internal documents) further describing our work with Ethicon in the late 1990's and an accumulation of knowledge over the past 7 years. This article describes in detail the necessity of large pores (> 1mm), foreign body reaction, tissue response/integration, complications, biomechanical properties, biocompatibility, and the concept of fibrotic bridging. [91]

11. 2006: Cobb articles (cited abundantly by Ethicon in their internal documents) repeating that <1mm leads to fibrotic bridging and cites our earlier work. [57,19]

12. 2006: "GPS for Pelvic Floor Repair" (Prolift physician sales brochure) states: "Amid Type I Mesh; Knitted monofilament does not potentiate infection; large pore size fosters proper tissue incorporation; lightweight, soft, and supple – constructed of reduced diameter fibers knitted into a unique, patented design with approximately 50% more flexibility than standard PROLENE Polypropylene Mesh". Again, employees at Ethicon are inexplicably unaware of critical data generated as a result of their work in Europe developing the large pore concept of >1mm. [92]

13. 01-26-2006: Ethicon Corporate Product Characterization analysis by Dan Burkley of Prolene Soft porosity showing variation between 0.29 and 2.38 mm. [93]

14. 2006 (?): Robinson's (unsigned) Clinical Expert Report "Ultrapro Mesh for POP Repair through a Vaginal Approach" (undated, but the metadata says it was from 2006) wherein Dr. Robinson utilizes the same Cobb quote from 2005 article stating <1mm leads to bridging fibrosis; has the same picture of fibers surrounded by FBG's that are in Cobb articles; and, lists Prolene Soft pore size from 0.3-2.4mm, confirming Burkley's findings above and stating in the "Summary" section that "a suitable mesh should offer a pore size >1mm and feature lightweight properties to avoid the occurrence [of] scar plate formation.". This Clinical Expert Report concluded that Ultrapro's design properties made it suitable for PFR. It is interesting that this appears to be a draft of what ultimately was Robinson's Clinical Expert Report for Prolift+M. In his two signed Clinical Expert Reports for Prolift+M and Prolift, he never mentioned pore size again nor did he mention how it relates to bridging fibrosis nor did he include the chart of various products and their pore size which showed the variability of Prolift from 0.3 – 2.4mm. [94]

15. 06-02-2006: Minutes from Ethicon Expert Meeting where Klosterhalfen makes important points regarding biological response. [95]

    a. More than 300 m of suture material gives meshes a huge surface area;
    b. Even after 20 years, the tissue is still reacting to the mesh;
    c. Fibrosis is responsible for complications in mesh usage;
    d. There is less fibrosis with Vypro compared to PP;
    e. Foreign Body Reaction:
        i. Fibrinogen and albumin bind to biomaterial, change and active the immunologic system;
        ii. Active process, a "chronic wound", to be demonstrated by proliferating and dying cells;
        iii. Combination of material and genetics;
    f. Optimum pore size is material dependant (critical pore size; at least 1-2mm), scar formation a combination of pore size, surface area, polymer;
    g. Large pores: Fibrosis on the mesh fiber only;
    h. Small pores: Interconnection between mesh pores due to fibrosis leading to mesh shrinkage;
    i. Provided same diagram (depicting fibrotic tissues surrounding mesh fibers with no bridging in large pores and bridging effect in small pores) used in Robinson's unsigned Clinical Expert Report and similar to diagrams in Cobb literature from 2004/2005;
    j. Shrinkage of 20% with reduction of mesh area to 64%;
    k. Mesh is fixed in tissue within 1-3 days;
    l. Monocryl causes less inflammatory response compared to Vicryl;
    m. Tension of the mesh changes pore size;
    n. Meshes can cause nerve damage due to mechanical irritation (mesh bears on nerve);
    o. There is no inert material.

16. 06-14-2006: Email string re "Mesh Microns" between Scott Ciarrocca (Ethicon R&D) and others stating "Pore size in microns was not measured during the development of the PROLENE Soft Mesh….Since the product construction results in irregular pore geometries and sizes, it is not accurate to report a distinct pore size." [96]

17. 07-2006: Weyhe article that lightweight does not necessarily mean fewer complications. As he correctly notes, larger pore size is the most important design factor re complications, more so than the "weight" of the mesh. [57]

18. 02-23-2007: Minutes from Ethicon Expert Meeting [97]:

Klosterhalfen

- Textile structure of the mesh – pores and knitted construction – is more important than the area weight. Terms "lightweight and heavyweight" may be misleading;
- Optimum pore size: macrophages reach everything, they immigrate into the nods;

Spychaj

- In pelvic floor surgery, shrinkage seems to be more important than in hernia surgery;
- Discussion about model for pelvic floor: no adequate animal model in this case;
- Might an abdominal wall model be a better solution? – No agreement about that; Objection: there is no real fascia in the pelvic floor;
- Shrinkage is not controlled by "softness" of mesh;

Cosson

- Questions if PP is the best material as fractures are observed in PP after time;
- PP meshes might not be improvable in terms of shrinkage; we may need a completely new material.

19. Spychaj PowerPoint from 2-23-2007 Ethicon Expert Meeting "Factors Related to Mesh Shrinkage" stating "Pore size: Small porous meshes (<1mm) lead to 'fibrotic bridging' → increased shrinkage; Large porous meshes allow for a better and faster tissue ingrowth → less shrinkage/contraction" with same graphic from Klosterhalfen expert meeting. "Intensity of FBR (Foreign Body Reaction) Quality and quantity of FBR are directly related to mesh type; Excessive FBR → massive scar plate → more shrinkage". [98]

20. Volpe PowerPoint "R&D Perspective – The Journey from Prolift to Prolift +M" ; slides with same drawings and same conclusions as Klosterhalfen, Spychaj and Robinson: [99] [Fig. 13]

a. Key unmet needs – pore size, more closely match native tissue;
b. Pore size – pre-clinical studies have reported 'that the greater distance between pores resists the ability of bridging fibrosis, contributing to improved compliance and less passive compression of the Biomaterial' citing Cobb (2006);
c. Denotes superior attributes of Prolift +M vs. Prolift regarding the increased pore size, increased flexibility and decreased density of +M;
d. States that Prolift +M was "designed for increased biocompatibility with the vagina…prostheses used to treat POP should have mechanical properties closer to those of vaginal tissue";
e. "Shrinkage – definition: It is not the mesh that shrinks, but the surface reduction is due to a simple retraction of the fibrotic scar tissues around the mesh." cites Klosterhalfen (2005) and Cobb (2006);
f. Highlights the optimal features of Prolift +M as providing resistance to wrinkling, folding and wound contracture; integrates into a soft, flexible scar; minimal FBR during remodeling phase; large pores that minimize scar bridging. Cites Cobb (2005).

21. 03-28-2007: Vailhe Technical Report comparing UltraPro and Gynemesh PS to competitors. Table 12 [100] shows "Average Pore Size (mm)" for Ultrapro as 2.5-3.5mm and PS as 2.5mm (which does not correlate to Burkley's analysis of pore size ranges from his testing on 01-26-2006. Also gives "Average Porosity (%)" for Ultrapro as 69.2% and for PS as 65.6% (which does not correlate with his testing in 2002).

22. 08-23-2007: Zaddem email to Robinson citing Cobb and Klosterhalfen stating that according to these references, "> 1mm is needed to prevent bridging fibrosis" [101]. However, Ms. Zaddem testifies during her deposition that "I remember this being specifically documented by medical affairs, that the pore size needs to be greater than 75 microns, and this is larger than that" This information was given to her when she questioned the size during development of Prolift +M [102].

23. 11-18-2008: Ethicon PFR online training course, while referencing my publication, [103] states:
    a. Understanding mesh contraction or shrinkage
        i. Any wound shrinks while healing whether mesh is implanted or not
        ii. Increased inflammatory reaction may be responsible for mesh shrinkage
        iii. Reduced foreign body reaction is association with less mesh shrinkage
        iv. Observed in meshes with pore sizes of less than 1 mm
        v. Can be minimized by reducing the inflammatory reaction with well tolerated mesh material with large pore size
    b. Mesh Pore Construction
    c. Pore size relates to handling properties and to the ability of the mesh to interact with the tissues in which it is implanted.
    d. Pore size > .75mm;
        i. Translates into tolerance by tissue ingrowth and admission of fibrobloasts, macrophages, leukocytes, and collagen fibers into the mesh structure
        ii. Promotes integration of the mesh into the normal tissue architecture

iii. Prevents the formation of rigid scar plates that may cause deformation of the repair site, bunching of the mesh, pain and decreased mobility

It is inexplicable that Ethicon could cite my article as a basis for claiming to surgeons or other physicians that adequate pore size is >.75mm. Presenting this false information is misleading.

24. 4-22-2009 Holste email to Meek "The border for scar plate formation in small pore standard weight meshes was set around 1000 microns". [104]

25. 01-17-2010: Hinoul email re meeting with Klosterhalfen, calling him "the god of surgical pathology on the subject of textile implants in this solar system" re necessity of pore size >1mm. [105]

26. 02-17-2011: Zaddem email [106] to multiple people (including Kirkemo) regarding mesh pore size and how it relates to tissue compliance and contraction. She again block quotes the Cobb article but also block quotes a cite from Deprest in 2006 saying that macroporous = >75 microns!! Inconsistency and poor understanding of the design issues continues to be a pattern throughout Ethicon's documents. There is also an extensive list of complications that can result due to inadequate poor size; how ironic that Ethicon would be so assertive as to pore-size-related complications, yet be so misguided as to sufficient pore size to avoid those very same complications.

Sworn Testimony Ethicon Employees

Piet Hinoul – WW Medical Affairs [107]:

- "...we have only meshes that... have large enough pores that allow that mesh incorporation into the tissue." States that pore size is a very important aspect of the Prolift.
- "I am sure that we've done a lot of preclinical work in which we have explanted the mesh and measured the pores. I just cannot give you the exact data on that."
- When asked if the larger pore size of Ultrapro was thought to be a benefit: "Yes. By reducing half of the amount of polypropylene, which is the component that stays behind in the body, you automatically have to reduce the pore size, yes."
- When asked if Ethicon believes that there is significance to a pore size of 1 millimeter: "I do not know where 1 mm comes from as a reference". When asked his understanding of effective porosity: "So my understanding of effective porosity is -- how will I say it? Yeah, I don't know. I'd have to guess."
- "Ethicon medical affairs relied on what was known in the scientific community that you had to use macroporous meshes larger than 70 microns. That is well established fact."
- When asked what happens to the pore size of mesh after implantation he stated "So, in the majority of patients the change would be zero percent" and "It is hard to predict...the mesh in itself doesn't shrink. That also means that the pore size is not affected. It is the

scar around the mesh that could possibly make it contract. If you would explant it at that stage and get rid of all the scar on the mesh, you will get back to a 4-millimeter or, you know, whatever the pore size was initially."

- Dr. Hinoul demonstrates the confusion in Ethicon medical affairs as to adequate pore size. When asked about Dr. Robinson's document wherein he stated that 1 millimeter is required to avoid fibrotic bridging, Dr. Hinoul states: "We're consistently referring to the 1 millimeter where I disagree that I haven't seen that reference in the evidence-based literature... And I keep going back to the Amid classification of a macroporous mesh."

David Robinson – Medical Affairs Director [108]

- Dr. Robinson testified that at the time of the 2006 Expert Meeting, Ethicon was aware of the proper pore size needed for macrophages to go through the pores, which according to him, is 75 µm.

Scott Ciarrocca – Associate Director, R&D; Team Leader Project D'Art (Prolift) [109]

- Mr. Ciarrocca refers to the pores as "air gaps" and when asked if he had an understanding of whether the size would affect performance, he testified: "Again, no, I didn't have any particular understanding as it relates to the size of air gaps."

- Mr. Ciarrocca testified that he never had any understanding as to whether the pore size in Prolift could impact safety and efficacy, and that was never evaluated as part of the Prolift project.

- Pore size was not a part of the design verification for Prolift; Ethicon did not do any testing to establish pore size, but he believes that would have been done for Gynemesh PS (Prolene Soft Mesh).

Sean O'Bryan – Regulatory Affairs:[110]

- Testified that small pores allowing for an interconnection between mesh pores due to fibrosis leading to mesh shrinkage would be undesirable and unsafe.

x. Bacterial Adherence/Entrapment

An optimal mesh design for pelvic floor repair should not only be mechanically strong and pliable and encourage strong tissue ingrowth while minimizing FBR, it should also have the ability to resist infection. Acute and chronic infection lead to poor tissue integration and in many cases, require revision surgery. Post-implantation bacterial colonization is one of the major reasons for the slow and, at times, inadequate integration of surgical implants in the pelvic floor. [Fig. 14] Thus, the ability of a biomaterial to resist infection has important clinical significance. [111]

Vollebregt et al. demonstrated that 83.6% of the pelvic meshes in their study were colonized by different types of bacteria. In that study, 96% of the mesh arms were colonized.

An important finding from that study was that repeated disinfection of the surgical area just before handling the mesh did not alter the colonization rate and type of cultured microorganisms. These authors felt that long-term safety data with respect to the risk of infection and erosion in vaginal surgery was still lacking. Furthermore, this study clearly shows that in contrast to the use of meshes in the abdominal wall, contamination has to be considered as a rule when using meshes in the pelvic floor. The potential for increased risks when using alloplastic meshes in a contaminated field should demand further and intense investigations. [112] Although Vollebregt et al. attempted to alter the mesh colonization by repeated disinfection, Culligan et al. Found that it is impossible to truly sterilize the vagina before surgery because it is laden with normal inhabitants. [112a]

Boulanger et al. performed bacteriological analysis of explanted slings and pelvic meshes and published their results in 2007. The most frequent cause for the removal of these meshes was symptomatic vaginal erosion (62%). Bacterial contamination was found in all meshes, two of which were Prolene Soft slings and Gynemesh PFR mesh. Infections were multimicrobial in 31% of the meshes. Progression of infection on the explanted mesh was thought to be explained by the transformation of bacteria in virulent colonies adhering to the fibers. They saw increased rates of infection in mulifilamentous mesh due to the increased surface area offered to the bacteria. With pore areas less than 10 µm, bacteria (<1µm) are small enough to colonize while macrophages (16-20 µm) and leukocytes (9-15 µm) are unable to penetrate the interstices of multifilaments. As such, they concluded that large pore, monofilament, PP meshes have superior resistance to bacterial infection. A second mechanism of infection discussed by Boulanger is linked to the adaptive mechanisms of the bacteria itself. The virulence of certain bacteria may be explained by a production of a "slime" or "biofilm" around bacteria colonies. These biofilms will allow the bacteria to remain silent for some period, but over time, they can begin to multiply if an intervening event happens such as alteration of host immune defenses. Chronic infections can thus show up several months or even several years after implantation. [38]

In the 2/28/05 DDSA regarding "Mesh Contamination" , the Prolift design team did not properly assess the "Probability of Hazard" as to whether the Prolift device was susceptible to mesh contamination. The comment to this risk assessment merely stated "acceptable surgical practices should be followed in the presence of infected or contaminated wounds." [114] In light of the Vollebregt study referenced above, the suggested mitigation of this hazard would fall short of preventing the risk of a contamination. Failure to properly assess the risk of mesh contamination during the procedure *and* post-implantation was a critical flaw in the design team's risk assessment.

Dr. Hinoul testified that: "...Indeed, the chance of introducing a bacteria in that mesh or in that wound is a possibility and, therefore, you have to be extra careful and your meshes must be -- must have a product requirement that even when they get infected, that antibiotics and your immune response can clear of that infection." [115]

Johnson & Johnson's outside consulting group, PA Consulting addressed numerous safety concerns regarding the bacterial contamination of meshes in their extensive study of May 18, 2011 [116]:

- Inserted transvaginally, mesh traverses the vaginal area that carries many bacteria, hence, without protection, it is virtually impossible to insert mesh devices without contamination;
- Host cells and bacteria compete for dominance over the mesh surface. If the latter prevail the mesh is irreversibly contaminated and the bacteria may remain dormant for long periods, with the possibility of establishing a tissue infection later;
- Mesh surface area may thus be significant in infection rates as it provides a greater potential for bacterial attachment;
- Following insertion, there is a 'race for the surface' of the mesh between host cells and bacteria. If the bacteria colonize the surface, they protect themselves with a biofilm, preventing host defenses from eliminating them
    - The graft area is irreversibly contaminated and the bacteria may remain quiescent for long periods of time, and
    - Surface area is thus important owing to the large area available for potential bacterial attachment
- Pore size is significant
    - > 75 µm allows for greater tissue in-growth
    - < 10 µm interfere with host defenses and discourages small blood vessel in-growth
    - WBC are 9-15x bigger than bacteria, hence the latter can invade spaces not accessible to the former
- In the areas where the fibers are linked to each other the filaments form multifilament bundles and the tiny loops and interstices may favor harboring bacteria.

xi. Shrinkage

Mesh contraction, also known as mesh shrinkage, is a common phenomenon after mesh implantation which is closely related to fibrotic bridging. [Fig. 15] Mesh shrinkage can be defined by a reduction of the surface area of the original implanted mesh. The surface reduction is due not to shrinkage of the mesh fibers themselves but rather to a retraction of the fibrotic scar tissues around the mesh. Retraction of the scar is a physiologic reaction of maturing scar which is characterized by a constant water loss and, consequently, a subsequent surface area decrease to an average of 60% of the former wound region. It is known to take place in the first few weeks after implantation but can last as long as 12 months or more after surgery. [Fig. 16]

In 1997, Amid reported findings of mesh shrinkage in explants of approximately 20% at 10 months after implantation. That same year, we published a case report of Prolene mesh shrinkage (30%) resulting in a secondary hernia and chronic inguinal pain after a TAPP procedure. [66, 69] [Fig. 17]

The following year, we reported on the shrinkage of PP mesh in vivo in an experimental animal study comparing Marlex (heavyweight) to Vypro (lightweight). What we found was that PP meshes shrink to about 30-50% of their original size within 2-6 months after implantation

(lightweight 34%; heavyweight 46%). Our results supported the theory that the amount of mesh contraction depends on the extent of inflammation and scar formation resulting from the design of the textile implant (amount of material and pore size).

Cobb et al. reported in 2004, that they found no significant difference in the degree of shrinkage between various mesh devices regardless of the weight. The percentage of contraction for the three weight classes they tested were lightweight (Ultrapro) 29%, medium weight (Prolene Soft) 33%, and heavyweight (Marlex) 28%. [19]

Cobb again reported on mesh shrinkage in 2005 stating in his publication, "one concern with the long-term implantation of mesh is the amount of shrinkage…the material undergoes. All available meshes, regardless of their composition, experience a 20-50% reduction in their initial size. Factors of the mesh itself and the surrounding tissue inflammatory response contribute to this phenomenon." [57]

In 2007, Tunn et al. also found considerable mesh contraction after pelvic floor repair with PP meshes. They compared the initial length of implanted mesh (Prolift (Ethicon) and Perigee/Apogee (AMS) and the sonographically measured mesh length six weeks post operatively. Their results demonstrated a decrease in the mesh length of 60% for anterior meshes and 65% for posterior meshes. They also found that the mesh supported only 43% of the length of the anterior vaginal wall and 54% of the length of the posterior wall. [117]

More recently, in 2010, Velemir et al. also did an ultrasound study of mesh shrinkage and its possible relationship to the mechanism of recurrence after transvaginal mesh repair of anterior and posterior vaginal wall prolapse with Prolift. At the ≥ 1 year follow up, 12% of the patients in the study group presented with recurrence of vaginal wall prolapse. Contraction of the anterior mesh was found to be absent in 8 (10.7%) of the patients moderate in 60 (80%) of the patients and severe in 7 (9.3%) of the patients. It should be noted that one of the authors of this article is Dr. Bernhard Jacquetin, the founder of the TVM technique and long-time consultant to Ethicon and a contributor to the paper was Dr. Piet Hinoul, Medical Affairs Director, Ethicon. [118]

Also in 2010, Letouzey et al. found that there is a gradually higher amount of contraction at 3, 6, and 8 year follow up. This suggests that there may be progressive shrinkage and that mesh contraction syndrome will continue indefinitely. [111]

The use of ultrasound to determine how mesh will react in vivo was discussed several times during development of Project Thunder. In 2007, it was stated that the "3D Ultrasound is fascinating, dynamic means of evaluating meshes in vivo and shall be included." [119] It was decided that the Project Thunder team would begin training for ultrasound use in 2008 with Dr. Kociszeski. [120] Then, during in email chain later that year, Dan Smith, an Ethicon employee stated that Dr. Kociszeski was brought into Ethicon a year prior [121]. It seems as though no further development was made on the use of ultrasound to study mesh characteristics after implantation.

In April of 2007, Dr. Kerstin Spychaj, Ethicon R&D prepared a paper entitled, "State of the knowledge in 'mesh shrinkage' – What do we know?" Spychaj does a literature review which includes many of the conclusions listed in the paragraphs above and concluded that the "ideal mesh" in order to avoid shrinkage would be a lightweight material (partially absorbable) with a pore size > 1mm and mild but not excessive FBR and wound contraction with swift and adequate tissue growth. [122]

Not only had Ethicon determined that shrinkage was obviously critical to the quality of its mesh products, they knew it could cause "vaginal anatomic distortion which may eventually have a negative impact on sexual function." Furthermore, they knew "its treatment is difficult." [123]

Despite Ethicon's apparent knowledge of the significant amount of mesh shrinkage in their products, the potential causes of mesh shrinkage as well the resultant patient complications that could occur as a result of said shrinkage, they did no testing nor made any design changes to Prolift in order to reduce the occurrence of this known and serious complication. Failure by Ethicon to properly study and/or make the necessary design changes to avoid this hazard was improper, irresponsible and diminished patient safety.

Sworn testimony of Ethicon Employees

David Robinson - Medical Affairs Director: As to what was known about shrinkage of Prolift: "Any mesh will contract, yes."; It simply means that the mesh doesn't shrink, but as ingrowth of tissue occurs into the mesh, the entire mass will contract some."; "Actually, the exact percentage wasn't known for sure."; and "Well, we hypothesized that it would shrink or contract in the 30 percent range." [124]

Scott Ciarrocca – Associate Director R&D, Team Leader Project D'Art (Prolift): The design (of Prolift) was not modified in any way in response to the risk of contraction. [125]

Aaron Kirkemo - Assistant Medical Director: States the he is unaware of nerve entrapment and neuroma formation in the event of mesh roping. [126]

Sean O'Bryan, Senior Project Manager, Regulatory Affairs, testified that the extent of Ethicon's knowledge as to scarring and implant shrinkage, if it could cause injury to the patient, should be conveyed to the physicians in the product's Instructions for Use and should be conveyed to the patients receiving the products. [127]

Aaron Kirkemo, Medical Affairs testified that "There is no way -- and, again, there is no way that I'm aware of that you would be able to assess for it, like immediately after the operation. The material is not radio opaque. You can't see it with x-ray. You can't see it with CT. You can't see it with MRI". [128] According to Ethicon's internal documents listed above, this was and is obviously not the case, and Dr. Kirkemo, Ethicon's Director of Medical Affairs appears to be misinformed.

xii. Fraying/Particle Loss

Prof. Mang investigated Prolift and Prolift+M to determine whether particulates (loose particles of mesh fibers) were detectable before handling, after attempts to detach fixed particles by rubbing or ultrasound, as a consequence of trimming the mesh by 5 cm incisions, or as a consequence of dynamic strain.

Fragments were detected at several points for Prolift and Prolift +M. Prof. Mang found that particulates were visible before any handling of the products occurred. It was also found that that fragments of polymer detached from the mesh during handling (e.g. shaking or rubbing the mesh). Mesh fibers were also seen after cutting of the mesh, a practice that is commonly used by surgeons. Finally, particulates were seen after repeated stretching of the mesh.

The fragments consisted of either fiber fragments (500 – 3000 µm) or of polymer particles (< 250 µm), that may be a consequence of mechanical damage to the textile structure either during manufacturing or during handling at the surgical procedure. More than 100 particles were detected during the testing of Prolift+M and over 500 particles were found with Prolift. The detection of these particles proves that the amount of polymer coming into contact with the pelvic tissue will significantly increase.

Whether this result is representative for all devices, or whether these particles in fact enhance the local tissue response needs to be clarified with further analysis. More probably than not, particulates of this nature will create a host defense response that includes the same series of cellular reactions as the main portion of the mesh. Also, more probably than not, particulates scattered throughout the pelvic tissue will create an inflammatory response of some magnitude; will increase the overall foreign body reaction and inflammatory response; will increase the amount of the fibrotic reaction; and will run the risk of migrating into other parts of the body. Before launching a product, particle loss should be studied and a standardized measurement determining an acceptable amount of particle loss should be developed. In 2000, surgeons advised Brigitte Hellhammer, an Ethicon employee, that Gynemesh surgical mesh "released particles that migrate through the vaginal wall causing pain during intercourse". This information may provide insight into the unstudied effects of particle loss in Ethicon's Prolift mesh. [128a]

Defragmentation of the mesh should be either avoided. As shown by Ethicon's decision to change their manufacturing process from mechanical cutting (TVT) to laser cutting (Prolift & Prolift+M), the relevance and importance of particle loss has already been acknowledged by Ethicon and should be further considered when evaluating potential design deviations.

As mentioned above, testing of the Ethicon meshes by Muhl demonstrated significant frayed edges of all the test samples. The frayed edges not only have a propensity to increase the inflammatory process in the tissues but also lend themselves to detaching from the body of the mesh implant during implantation as a result of the necessary surgical procedures as well as during the life of the product in vivo. As the frayed edges are subjected to the physiological forces of the pelvis, the concern is that particles will detach and contaminate the surrounding tissue, subsequently leading to an intensified inflammatory host defense response.

In 2003, Pariente published a study in which he evaluated the amount of material shed by different suburethral slings under certain test conditions. His study was aimed at determining whether, during the course of a sling procedure, particles would shed during surgical manipulation and end up in the surrounding soft tissues with an unpredictable impact on the ultimate success of the procedure. Because slings are cut from large rectangular blocks, he questioned whether small segments of material could be shed during and after load deformation. Dr. Pariente's conclusion was that "the very high particle shedding for both Sparc (AMS) and TVT (Ethicon) may be of significant long term clinical concern in some quarters." TVT had the highest percentage loss of initial weight at 8.5%. [129] Other authors have commented on the fraying phenomenon of Ethicon's TVT slings as well. [130]

In their Prolift IFU, Ethicon informs surgeons that "The mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. ***This construction permits the mesh to be cut into any desired shape or size without unraveling***." [8] (emphasis added) The Prolift surgical guide also presents cutting the mesh as an option where needed to trim the device. [131]

Mesh fraying was recognized as early as 2000 as a potential concern by Ethicon, beginning with its TVT products. In November of 2003, Marty Weisberg, who at the time was the Senior Medical Director of Gynecare, made a note to the TVT file indicating that there had been 58 complaints of mesh fraying since 2000. In that memo to file, he stated that "Fraying is inherent in the design and construction of the product. The mesh elongates in places; the mesh narrows in places; and small particles of Prolene might break off." He determined that the particles would not be of any risk to the patient. Their justification behind this untested assertion was that Prolene (PP) materials had been "tested for biocompatibility as part of the suture product line. The safety of the particles becoming implanted should be no different than implanting of the mesh strip." Dr. Weisberg determined, without any testing, that the fraying does not change the efficacy of the product. [132]

In a number of Ethicon documents, they deemed fraying and mesh particles as "non-reactive", [133] and determined that no corrective action needed to be made. However, Ethicon began the process of updating their manufacturing process to laser cutting the mesh instead of mechanically cutting the mesh in 2005. Laser cutting the mesh was intended to reduce particle loss, as well as to maintain maximum elongation properties. Despite their test results that one manufacturing process actually reduced particle loss and another did not, Ethicon continued to market both products. [134] This is surprising given the fact that Ethicon deemed elimination of particle loss as an important CTQ (Critical to Quality). [135]

In an internal Ethicon R&D paper in April 2007, Dr. Spychaj stated that "the edges of the implant should be smooth, and unraveling has to be prevented, because this may lead to an excessive inflammatory reaction." Dr. Spychaj concluded that because PP is warp-knitted, this change in textile construction prevents unraveling of the cut edges of the mesh. However, he cites no testing by Ethicon as a basis for this assertion. [122]

If fraying and particle loss have indeed been determined by Ethicon to be "critical to quality", then it would have been prudent of them to include fraying and particle loss testing in

their design verification process for Prolift. However, from my review of countless internal Ethicon documents, it does not appear that such testing was performed during the Gynemesh PS or Prolift design verification process.

Sunny Rha, Quality Affairs, was asked in deposition if there is a difference between laser cut and mechanical cut mesh [135a] she testified that: "If I put this -- when I got this mechanical cut and laser cut, when I put it in my cubicle in a folder, the mechanical cut had after a period of time when I pulled it from my plastic bag, there were mesh what is -- the mesh particulates, laser cut you didn't see it."

Dr. Robinson testified [136] Ethicon, in its training materials leaves it to the judgment of the individuals if and how to trim the mesh kit for proper fit.

5. CLINICAL OUTCOMES/COMPLICATIONS

Poor design leads to poor outcomes. Failure of a mesh manufacturer to properly and thoroughly identify and consider the relationship between the risk of complications and its relationship to design characteristics can have drastic, dangerous and life-changing consequences for patients.

Neither surgeons nor patients are charged with the responsibility of designing and testing surgical meshes in a safe manner or being apprised of the latest scientific knowledge regarding the relationship between reported complications and their relationship to potential product design defects; this burden and responsibility falls squarely, and justifiably, on the shoulders of the manufacturer. Likewise, it is the responsibility of the manufacturer, not the physician or the patient, to appropriately warn of the known or knowable safety risks that accompany a particular product.

Ethicon was aware that certain optimal design characteristics of pelvic floor meshes would lead to improved clinical outcomes in many patients. Ethicon's failure to make necessary design changes to avoid these complications made their pelvic floor repair product, Prolift, less safe to the patients in whom it was permanently implanted than had they given due consideration and acted with reasonable care in designing a safer product. If designing a safer pelvic mesh product was *not* possible, Ethicon had an obligation not to market the product. Had Ethicon acted safely and reasonably with regard to its design, manufacture and sale of its pelvic floor mesh products, serious harm and injury to patients could have been avoided.

When asked about complications related to Ethicon's pelvic meshes, Ethicon former Director of Medical Affairs, Dr. David Robinson testified at his deposition in this matter as follows: "Well, there's two parts that come into play here. Three, actually. One is the patient's characteristics; two is, as opposed to a pill that's taken by the patient and the doctor has no input, here a surgeon has significant input into the outcome of the surgery. And the third is the product itself. **So what we have to do is assure that our product, per se, meets the characteristics that we are describing it having**." [136] (emphasis added). In the event that an otherwise healthy patient suffers an injury after an operation that was performed properly, the only explanation for their injury is an inadequate design of the device.

Complications reported to FDA:

Following its Public Health Notification (PHN) in July 2011regarding surgical mesh for pelvic organ prolapse and stress urinary incontinence (which was the second PHN for these products in 2 ½ years), FDA held Advisory Committee meetings (AdCom) in September 2011 to address an increasing number of serious adverse events that had been reported and received in the MAUDE database. Prior to AdCom, FDA published the number and percentage of MDRs by adverse event that had been reported from 2008 to 2011. [137] They are as follows:

- **Erosion**: 528 cases reported, equaling 35.1% of all events
- **Pain**: 472 cases reported, equaling 31.4%
- **Infection**: 253 cases reported, equaling 16.8%
- **Bleeding**: 124 cases reported, equaling 8.2%
- **Dyspareunia**: 108 cases reported, equaling 7.2%
- **Organ perforation**: 88 cases reported, equaling 5.8%
- **Urinary problems**: 80 cases reported, equaling 5.3%
- **Neuro-muscular problems**: 38 cases reported, equaling 2.5%
- **Vaginal scarring/shrinkage**: 43 cases reported, equaling 2.8%
- **Prolapse recurrence**: 32 cases reported, equaling 2.1%

Because the absolute number of performed procedures is not known and the number of followed-up patients and the definitions of an event are not defined, this cannot reflect the true incidence; however, the FDA's review clearly indicates that there were serious complications being reported that should have been addressed by Ethicon as they were reported.

Complications reported in Scientific Literature:

In our publication in 2005, the data from the postretrieval study of over 300 explants showed that most explants from all of the patients with **chronic pain** in their medical history indicated nerve fibers and fascicles in the interface of the mesh. With the improved technology of immunohistochemical stains, we can now detect even the smallest nerve structures that are mainly found in or around the **foreign body granuloma**. Due to the nature of the granuloma as a chronic inflammation, most probably, these nerve structures are irritated by the **inflammation** and cause the sensation of **pain**. In some cases, evident **traumatic neuromas** can be found at the interface of the mesh-recipient tissues, an indicator of the mechanical **destruction of the nerve** by the mesh. [91]

Elmer et al. in a one-year, prospective, multi-center, cohort study of 232 patients in whom Prolift surgical mesh was implanted, found 11% **erosion**, 2.8% mesh **exposure** requiring surgical intervention. Severe **inflammatory reactions** were uncommon, yet mild-to-moderate reactions were significantly increased one year after surgery. "Randomized controlled trials are now needed to clarify how the risks and benefits associated with the use of synthetic mesh kits in prolapse surgery relate to patient satisfaction when compared with traditional prolapse repair." [138]

Elmer et al. in a small prospective study of 18 patients, ten of which were implanted with Prolift surgical mesh, evaluated the histological inflammatory response to the mesh. They found 30% mild **granuloma formation** and 20% mild **erosion**. Moderately increased postoperative counts of macrophages and mast cells found one year after surgery suggested that Prolift activates an enduring but "non-severe" cellular foreign body response in human vaginal submucosal tissue. Although they felt that the histological inflammatory results suggested satisfactory biocompatibility, they noted that "it is important to recognize that a large study population with transvaginal mesh surgery would undoubtedly generate an increased number of mesh related complications. Clinicians and patients should be aware of the possibility of late mesh related inflammatory reactions when using [Prolift]." [139]

Jeffrey et al. published a meta-analysis of safety and efficacy studies that were available up to December 2008 for surgical meshes to treat pelvic organ prolapse. Jeffrey analyzed 12 Prolift studies all with short follow up of a mean of 7.8 months. Reported anatomical **recurrences** in the operated compartment ranged between 1% and 16% for Prolift; however, when overall pelvic floor support was taken into account and **recurrence** in any compartment was considered, the **recurrence** rate went up to 30% for Prolift. Five of the studies that they reviewed reported at least 1 **bladder injury** associated with Prolift insertion. **Erosion** ("the most common adverse event occurring following the use of mesh in vaginal surgery") rates ranged from 2% to 10% with Prolift and de novo **dyspareunia** rates were reported between 15% and 17%. [140]

Blandon et al. did a retrospective analysis of patients referred to Mayo Clinic from January 2003 through September 2007 who had complications after vaginal placement of mesh. Complications included mesh **erosions (**57%), **dyspareunia** (47%), **chronic pain** (33%), **incontinence** (47%), **recurrence** (43%), and **chronic vaginal drainage** (43%). There was also **vaginal shortening** and **narrowing** in 48% of cases. 88% of the patients required some form of mesh excision, 75% required complete vaginal mesh excision. The surgeons pointed out in their publication that when mesh excision is warranted, **"tissue fibrosis, scarring, bleeding, and urinary tract and anorectal injury** are easily encountered, which add to patient morbidity." Significantly, these Mayo Clinic surgeons concluded that "As the use of synthetic materials in pelvic reconstructive surgery increases, so do complications specific to their use. Although the incidence of these complications is unknown, our series demonstrates that, when they occur, multiple interventions may be required and bothersome and occasionally life-changing symptoms may persist. Several concerning trends emerged from our study. Over half the women evaluated for mesh-related complications presented in just the first 9 months of 2007, which suggests that as transvaginal mesh use becomes more widespread there will be an increase in mesh-related complications." [141]

Kirschner-Hermanns et al. reported on their analysis of more than 200 pelvic floor mesh explants finding **erosions** of 66% in the small pore group and 41% in the large pore group; **chronic pain** and **nerve damage** with neuroma in 24% of the small pore group and 11% of the large pore group. The authors related the **chronic pain** and **nerve damage** to FBR and fibrosis which increased in the smaller pores. "CONCLUSIONS: Because of the marked **inflammatory** reaction of small pore structures, textiles with large pore should be preferred. However, the

materials have to withstand considerable mechanical strains, in particular without reducing its porosity. Standard polymers like PP and PET showed considerable high damage of structural integrity, which was not found with PVDF." [142]

Velemir et al. examined the **recurrence** at one year post-implantation of Prolift surgical mesh in 91 patients. **Recurrence** was found in 21%, 18% and 19% of women who had undergone anterior, posterior or total prolapse repair, respectively. Mesh **contraction** in the anterior compartment was found to be moderate in 80% of the patients and severe in 9.3% of the patients. Vaginal mesh **erosion/exposure** was found in 9.9% of the patients. The authors concluded that "**Recurrence** of prolapse after [Prolift] repair appears to be associated with **severe mesh retraction** and loss of mesh support on the distal part of the vaginal walls." One of the authors in this study is the founder of the TVM technique and long time consultant to Ethicon, Dr. B Jacquetin, and there was contribution to the publication by Dr. Piet Hinoul, Director of Medical Affairs at Ethicon. [118]

Binnebosel et al. published regarding the biocompatibility of prosthetic meshes in abdominal surgery. These authors conclude that the mesh-related chronic foreign body reaction seen in all implanted meshes is responsible for mesh-induced complications such as **mesh migration, adhesion, fistula formation**, and most importantly, **pain** and is therefore the limiting factor of mesh biocompatibility beyond the means of optimized mesh materials. Two-thirds of **recurrences** occur after 3 years (median, 26 months) suggesting that a technical error is unlikely to be the only cause of **recurrence** and that other factors may be equally important**. Mesh infection**, they state, is feared because it is difficult to eradicate without removing the mesh and can become clinically apparent many years after implantation. The risk of **infection** is mainly determined by the type of filament used and the pore size. **Chronic pain** is increasingly being discussed as one of the most important topics in the field of mesh surgery. **Chronic pain** following mesh repair is quoted with a risk of over 50%. The onset of **chronic pain** is typically more than 1 year after implantation. It is suggested that the **inflammatory** mesh response is an underlying pathophysiological mechanism for **chronic pain** after mesh implantation. In most mesh explants of patients with **chronic pain** in their history, never fibers are detectable in the mesh to host interface. Those nerve fibers are detected mainly in the **foreign body granuloma**, and due to the nature of a **foreign body granuloma** as a **chronic inflammatory reaction**, it is believed that these nerve structures are irritated by the inflammation, and thereby, cause the sensation of **pain**. Furthermore, as these authors point out, it has been speculated by Brown et al. that **chronic pain** could potentially be the result of a mechanical **destruction of nerves** by the mesh itself. [20]

Altman et al. published on the use of Prolift after 1 year. In their study of 389 women who were randomly assigned to a study treatment, 200 underwent prolapse repair with the transvaginal mesh kit and 189 underwent traditional colporrhaphy. At 1 year, the primary outcome was significantly more common in the women treated with transvaginal mesh repair (60.8%) than in those who underwent colporrhaphy (34.5). The surgery lasted longer and the rates of intraoperative **hemorrhage** were higher in the mesh-repair group than in the colporrhaphy group. Rates of **bladder perforation** were 3.5% in the mesh-repair group and 0.5% in the colporrhaphy group, and the respective rates of **de novo stress urinary incontinence** after surgery were 12.3% and 6.3%. Surgical reintervention to correct mesh

exposure during follow-up occurred in 3.2% of 186 patients in the mesh repair group. The authors concluded: "As compared with anterior colporrhaphy, use of a standardized, trocar-guided mesh kit for cystocele repair resulted in higher short-term rates of successful treatment but also in higher rates of surgical complications and postoperative adverse events." [143]

Withagen et al. compared the efficacy and safety of Prolift mesh repair to traditional repair. Results were reported of mesh **erosion/exposure** of 17% at 12 months. [144]

Abed et al. conducted a systematic review of Medline reports published between 1950 and November 2010 on adverse events after vaginal prolapse repair using graft materials. The incidence of **erosion** was 10.3% and **dyspareunia** 9.1%. [145]

Complications considered by Ethicon:

While trying to decide on the appropriate language for the "Adverse Reactions" for the Prolift IFU, there was an email exchange in July 2004 regarding mesh contraction/shrinkage. Axel Arnaud suggested adding "**mesh shrinkage**" as an additional adverse reaction in the Prolift IFU. **Mesh shrinkage** had not been included in the Gynemesh PS IFU. Sean O'Bryan, Ethicon Regulatory Affairs, stated that "If **mesh shrinkage** is a real issue, then we have an obligation to put it in." However, he also stated that if this new adverse reaction was added, Ethicon would also have to add it to the existing Gynemesh PS IFU as a modification. [146] Neither **mesh shrinkage** nor **mesh contraction** was added to the original or the revised Prolift IFU, nor was it added to the Prolift+M IFU.

At an "Ethicon Expert Meeting" in June of 2006, a number of outside expert consultants discussed complications of pelvic floor surgery using mesh implants. Dr. Cosson stated that **erosions** could affect the vagina, urethra, bladder or rectum, but was "not considered a big problem in the vagina (3% vaginal erosions with Prolift)." With regard to **infection**, he wondered if a low-density material would reduce the **infection** risk. With regard to **contraction** or **shrinkage**, Dr. Cosson said that he only had a "2.8% symptomatic contraction rate with Prolift." He also stated that "**chronic pain** is not a frequent complication – 1 case observed in 110 Prolift patients – yet it is the complication of most concern to surgeons."

At that same meeting, Prof. Klosterhalfen stated that "fibrosis is responsible for complications in mesh usage. There is less fibrosis with Vypro compared to PP." He also told Ethicon that **fibrosis** leads to **mesh shrinkage** and that this was seen in smaller pore meshes that were <1mm pore size. In the "Highlights" section of these meeting minutes, it is stated that "**more inflammation = more shrinkage**?!... One approach might be control of fibrosis and neoangionesis." Under the "Summary of Unmet Clinical Needs" section of the document the highest unmet need listed by the surgeons was "**no shrinkage/no long-term contraction; fibrosis reduction; less sexual pain; "severe contraction > dyspareunia > decreased sexual function**." Other listed unmet needs were "**no chronic pain", "less erosion", "no foreign body reaction", "less inflammatory response**". [95]

At a second "Ethicon Expert Meeting" in February of 2007, Kerstin Spychaj did a presentation in which he concluded "in pelvic floor surgery, **shrinkage** seems to be more important than in hernia surgery." Dr. Cosson added that "polypropylene meshes might not be

improvable in terms of **shrinkage**; we may need a completely new material". Also, the "Summary of Unmet Clinical Needs" from the Expert Meeting the year before was again confirmed without changes. [97]

In an Ethicon document entitled "WW Customer Complaints" from March 16, 2005 to July 10, 2008, a total of 231 complaints had been received on Prolift, 145 of these reported as "Serious Injury". The top complaints were: **mesh exposure (14%); erosion (12%); pain (12%); bladder perforation (9%); dyspareunia (5%); bleeding (5%); recurrence (5%).** Because Ethicon acknowledged that "It is obvious that in most cases the terms **'exposure', 'erosion', and 'extrusion'** are used interchangeably", the mesh **erosion** rate could be as high as 26% from this reporting. [147]

Ethicon used Prof. Klosterhalfen as an outside pathology consultant to do histological evaluations at the Duren Institute of Technology of explanted mesh samples received by Ethicon. As of April 2008, he had analyzed 100 such samples. At that time, he prepared an "Interim Report Mesh Explants Pelvic Floor Repair". Klosterhalfen reported to Ethicon his findings:

- Most serious complication following mesh implantation in pelvic floor was mesh erosion in 80 to 90% of cases. Most **erosion** is in nearly 100% combined with secondary mesh/surgical site **infection** SSI. Developing **mesh ulceration** follows this infection;
- All meshes without exception induce typical foreign body tissue reaction known from mesh implants with hernia surgery;
- Foreign body tissue reaction induces **fibrosis** in the mesh implant area, i.e. **severe FBR** is associated with **severe fibrosis**;
- **Severe fibrotic tissue reaction** is often associated with degenerative calcification;
- Small porous and heavyweight meshes or small porous and multifilament meshes induce **severe foreign body reaction** and **severe fibrosis**;
- **Neuromas** and neuronal proliferations induce **chronic pain**;
- Severe **fibrosis** is found in folded mesh implants with double layers. **Mesh shrinkage** and folding is obvious in pelvic floor repair.

His summary stated, "Foreign body tissue reaction followed by secondary **fibrosis** seems to play a special role in pelvic floor repair. This is important, because soft tissue coverage is thin in pelvic floor repair. Fibrosis and folding in this are inducing mesh **erosion**s and **ulcerations**". [148]

In June 2009, Prof. Klosterhalfen prepared another interim report regarding his histological examination of another 172 prolapse mesh explants. Some of his important observations were:

- Main complication still listed as **erosion** (80 – 90% of the explants);
- FBR is responsible for fibrosis at the implant site (strong **FBR = marked fibrosis**);
- **Strong fibrosis = degradation/calcification**;

- Small and medium pore, heavy and medium weight meshes were the most commonly explanted meshes and these meshes precipitate a strong FBR and fibrotic scarring;
- Strong fibrosis almost always leads to wrinkle formation in the mesh due to increased mesh **shrinkage**;
- **Shrinkage** leading to wrinkle formation is almost always detectable in the area of the **erosion**;
- **Neuromas = chronic pain at above-average rates**;

"In summary, therefore, FBRs and secondary fibrosis seem to play a significant role in prolapse repair… **Fibrosis** inevitably leads to mechanical irritation, particularly when wrinkling occurs, and should be seen as the basic cause of **mesh-induced erosion and ulceration**… **infection** is commonly observed following **erosion** in the vaginal mucosa." [149]

Evidently, **mesh erosions** were becoming such a problem with Prolift that Dr. Peter Meier, a Principal Scientist with Johnson & Johnson Medical in Germany, prepared a 122-page "Clinical Evaluation Report – Mesh Erosions" in September 2010. Some of the highlights are as follows:[150]

Mesh-Related Complications

"Once the mesh material has been implanted in the body, the host immune system reacts to the introduction of this foreign material and covers the material with a biofilm. This triggers a complex serious of host-to-implant material interaction. A typical inflammatory response is elicited which involves activation of the complement system, binding the antibodies, leukocyte formation, blood clotting, and fibrinolysis activation. This is followed by an acute inflammatory phase and a chronic inflammatory phase resulting in foreign body reaction; formation of granulation tissue with fibroblasts, macrophages, and neovascularization; and eventually foreign body giant cells and fibrosis.

"Mesh related complications may be associated with the mesh material used for reinforcement or the surgical procedure itself. Mesh material related adverse events include **infections, erosions, extrusions, mesh shrinkage, vaginal granulation tissue**… Additionally, functional problems such as **de novo urgency, urge incontinence, dyspareunia** and non-specific pelvic pain may also be observed in certain patient groups."

Etiology of Mesh Erosion

"**Erosion** means superficial destruction of a surface by friction, pressure, ulceration, or trauma. Mesh **erosion** refers to the breakdown of internal tissue caused by irritation or infection elicited by the patient's immune system when a foreign material such as synthetic mesh is introduced into the body. The exposed mesh may **erode** the vagina, urethra, rectum, bladder or bowel. Vaginal or urethral **erosion** phenomena may be related to poor incorporation of the mesh into host tissue, as a result of insufficient collagen synthesis (mainly produced by fibroblasts). The literature has noted **mesh erosions** to occur in 2.8% to 17.3% of pelvic floor reconstructive surgeries using synthetic meshes…**mesh erosions** can occur at variable times after implantation,

ranging from 6 weeks to 7 years." He further notes that **erosion**s can result in **vaginal pain, bleeding, discharge and dyspareun**ia. Vaginal **erosion**s have been seen to affect more than 10% of patients undergoing pelvic floor repair using synthetic meshes. [Fig. 18; Fig. 19]

Factors Affecting Mesh Erosions

The number one factor that Dr. Meier lists as causing mesh **erosions** is "pore size and porosity of the mesh." However, he uses the Amid classification of "macroporous" and states that "mesh materials having pore size greater than 75 microns" facilitates migration of macrophages and leukocytes and thus allows tissue ingrowth. "This property has been seen to reduce the infective risk, which is a predisposing factor for mesh **erosion**." He also states later in his report under the section "Prevention of Mesh **Erosions**" that pore size larger than 75 microns will reduce the incidence of **mesh erosions**. [150]

As mentioned earlier in this report, in May 2011, Johnson & Johnson retained the services of PA Consulting Group to investigate **mesh erosion**. One of the things Johnson & Johnson asked these outside consultants to analyze was Dr. Meier's report from September 2010. In a 50-page report, PA Consulting made the following observations/conclusions: [116]

- **Mesh erosion** is complex and the clinical studies do not give a clear picture, due to the diversity of the variables;
- **Mesh erosion** is difficult to model in vitro or in pre-clinical studies; and it is difficult to study the clinical effect of product changes;
- Of the many variables that influence **mesh erosion**, pore size is listed first;
- Transvaginal implantation has a higher risk of **mesh erosion** than trans-abdominal surgery;
- Vaginal area carries many bacteria, so it is virtually impossible to insert mesh devices without contamination;
- If host cells cannot clear the bacteria on the mesh surface, the mesh is irreversibly contaminated and the bacteria may remain dormant for long periods with the possibility of establishing a **tissue infection** later;
- Following insertion, there is a 'race for the surface' of the mesh between host cells and bacteria. If the bacteria colonize on the surface they protect themselves with a biofilm, preventing host defenses from eliminating them
    - The graft area is irreversibly contaminated and the bacteria may remain quiescent for long periods of time, and
    - Surface area is thus important owing to the large area available for potential bacterial attachment
- "Pore size is significant (citing an article by White, et al. from 1981) – Greater than 75 micron allows for greater tissue-ingrowth."
- PA Consulting spends 10 pages talking about how mesh production processes may influence the risk of **erosion** based upon numerous high magnification photos of Ethicon's pelvic mesh fibers showing "Artifacts on the filament surface… Competitor samples appear not to have the same artifacts – we scanned the filaments".

Following the FDA AdCom meetings in September 2011, Ethicon prepared a paper entitled "Polypropylene Mesh for Pelvic Floor Repair (PFR) – Focus on Mesh Exposure – Road to Improvement" prepared by Chris Vailhe on October 14, 2011. [151] In the paper, after noting the above-listed reported complications, Vailhe chose to focus the majority of the paper on "mesh exposure" as it was the highest percentage of adverse events. It is noteworthy that FDA listed the number one adverse event as "erosion", not "**exposur**e". Although this vernacular has been debated, **erosion** denotes an ulcerative process in the endothelial tissue of organs whereas exposure refers to mesh penetrating the tissues in which it is implanted and/or adjacent organs. It appears as though Ethicon seemed to be downplaying the very serious condition of the **erosion** of pelvic tissues by focusing on a different process, and less injurious-sounding term, "**exposure"**.

Nowhere in the paper does Vailhe analyze the adverse event of either **pain** (only 3.7 percentage points lower than erosions in the FDA report or infection, the third highest reported adverse event to FDA. By focusing on merely one adverse event and couching the event in a less severe manner before analyzing its level of potential harm to patients, Ethicon failed to properly address a number or serious and reported complications occurring in patients who received their products; not only when they were received, but also after they were brought to light by FDA.

Arguably, this should not have been the first time Ethicon did a thorough review of complications being reported in connection with the implantation of its pelvic floor mesh in women with pelvic organ prolapse; quite the contrary. If Ethicon was aware of complications with its products that could be attributed to design characteristics, Ethicon has a duty ***prior*** to launching its pelvic floor repair product, to do the necessary design testing, in order to ensure that the product is safe for implantation in women. At the very least, once Ethicon became aware of post-market complications being reported with their pelvic floor products, even if they had previously not anticipated these complications, once reported, immediate action would be expected. Different causes of these complications should have been explored: focusing on the indication to exclude poor healers, improving the training to reduce technical faults, or modifying the design to optimize biocompatibility. Neither version of the Prolift IFU has been appropriately modified, nor has its use been appropriately limited to highly-skilled surgeons, nor have the obvious flaws in Prolift's design been appropriately addressed in further activities.

Ethicon Claims that all Mesh Complications that are Known Today were Known to them when Prolift was Launched in March 2005. Their WW Medical Director testified that "…there are no new adverse events that we weren't aware of at the time of launch [of Prolift]." [152]

6. ALTERNATIVE DESIGN – "PROJECT THUNDER" & "PROJECT LIGHTNING"

In 2000, Ethicon sought and obtained 510(k) clearance for Pronova – a blend of PVDF and co-hexafluoropropylene for use as a suture material in cardiovascular, ophthalmic and neurological procedures. [153]

In 2001, Dr. Bridgette Hellhammer authored an internal document titled "Meshes in Pelvic Floor Repair – Findings from literature review and interviews with surgeons". Dr.

Hellhammer indicated that the surgeons that she interviewed were experiencing erosions in approximately 10% of the repairs utilizing mesh. Of the surgeons who had experience with Prolene or Gynemesh, they were concerned about the following perceived problems: the mesh was too thick and bulky; too stiff; releases particles when cut; and erosion rates similar to other synthetic meshes. Her conclusions were that a pelvic floor repair using a mesh implant was plausible, and "A thinner mesh than the current Prolene mesh and with some elasticity would be well accepted. Vypro would meet these requirements. A totally nonabsorbable mesh with similar mechanical properties as Vypro would also be well accepted." [154]

For almost all of 2002, Ethicon in conjunction with Prof. Klosterhalfen, performed morphometric and immunohistochemical comparative analyses of a Prolene mesh and a Pronova mesh. The Test Report B0086/02 indicates that the testing was monitored by Dr. Joerg Holste of Ethicon. Although the Pronova mesh featured better biocompatibility in the early phase of follow up compared to the Prolene mesh, the report states that this advantage disappeared during the ongoing course of implantation. [155] In that same year, Ethicon obtained a German patent No. DE 10043396C1 20.06.2002 for a PVDF surgical implant. [156]

In March 2004, Vincenza Zaddem, the Prolift Team Lead send an email to the Project Manager, Scott Ciarrocca, asking what type of mesh would be used for the Prolift and suggested: "hybrid mesh - was this considered? - midline section has a different weave/pore size and/or material (flexibility and elongation different) from straps or lateral sections; woven together - absorbable mesh on laterals for better realignment in lateral repair; laterals more flexible than midline - non-abs at midline for load bearing needed in apical repair; also to lay flat better." [157]

In an email exchange between Gene Kammerer and Kelly Brown in January 2005, Kammerer shares with Brown a conversation that he had with Prof. Mauro Cervigni (gynecologist), wherein Prof. Cervigni expressed his concerns about the results and complications he was experiencing with Gynemesh for "tension free" PFR. According to Kammerer, Cervigni was experiencing infection (8%) leading to erosions, erosions (8-10%), dyspareunia, contraction causing pain, sexual discomfort, "balling up" of the mesh, and recurrence. Kammerer suggested that Ultrapro mesh had design characteristics that could reduce erosion and contraction and that it should be marketed for PFR. In her response, Ms. Brown thanked Mr. Kammerer for his suggestion and said perhaps they could include Ultrapro "in our battery of samples at some stage". [158]

It is unclear why Gynemesh PS was chosen for the Prolift, other than, as certain Ethicon employees lamented, it was "pre-ordained". [159]

The physicians who developed the TVM technique (Cosson and Jacquetin), were aware of the complications associated with Prolift mesh and implored Ethicon to consider a different mesh material in 2004, before Prolift was launched for sale. Ethicon employee, Bob Roda, indicated on January 24, 2006 that after his meeting with the TVM group in Paris, "the group is strongly looking forward to a potential for materials for the Prolift product. Their main concern is the[y] believe that the Prolene Soft material over time contracts. Thus creating the potential for failures and/or erosions…an example could be a hybrid mesh that combines both absorbable and non absorbable material."

Another Ethicon employee, Gene Kammerer, responded two weeks later on February 13, 2006:

> As you know we are focusing on the active mesh project with the collagen and synthetic formulations on both PS and UltraPro. These are longer term solutions and provide significant benefits for enhancing meshes by potentially, and much longer term, including growth factors, signaling proteins and other materials into carrier scaffolds.
>
> A shorter term solution, as defined by the mesh team last year, was to substitute the UltraPro directly for the PS. Some European surgeons are already doing this and Axel had identified a couple. A moderate term solution was to change the knit construction of the UP to be more like the PS or alternatively substitute some Monocryl fiber into the PS. The benefits here are less material left behind, eventually; a low foreign body response with Monocryl vs Vicryl; no negative baggage associated with the Monocryl in pelvic floor; as with Vicryl; as a short, relatively, discovery and development time, as well as a more straight forward regulatory path, which we have already investigated.
>
> I met with both Dr. Cosson and Prof. Jacquetin at the Paris meeting in 2004. They expressed an interest in a new mesh to control and reduce scar contraction. This led us, Axel and I to investigate, the UP vs PS conversion. The results of the investigation showed us that it could be done and we could possibly get an enhanced product. The team wanted to move forward, but then everyone got re-assigned, and so the project kind of went into limbo. [160]

It was well understood and recognized that the complications associated with Prolift mesh were occurring frequently enough to validate the need for a new material. The development of Prolift +M, a device utilizing a new material and new design for pelvic floor repair, eventually became known as "Project Lightning" and began in early 2006. [161]

Complications, unmet clinical needs, and potential materials to be used for the new generation of Prolift were discussed during the June 2, 2006 "Ethicon Expert Meeting" in Norderstedt. The participants included Prof. M. Cosson, Prof. B. Klosterhalfen, Prof. J. Deprest, Prof. B. Jacquetin, Dr. V. Lucente, and Dr. Vierhout, as well as several Ethicon employees. During this meeting, Pronova (PVDF) + Monocryl and UltraPro were suggested as an alternative to PS. "Fibrosis is responsible for complications in mesh usage. There is less fibrosis with Vypro compared to PP… Monocryl causes less inflammatory response compared to Vicryl." Prof. Jacquetin stated that it "could be interesting to use Vypro in Prolift". At the end of the report it states "The usage of UltraPro in Prolift was fully supported by V. Lucente. M. Cosson and B. Jacquetin like the idea, however would like to have some clinical data before supporting it." [95]

At the "Ethicon Expert Meeting" on February 23, 2007, also held in Norderstedt with essentially the same participants as the year before, again alternative meshes for PFR were discussed. Peter Meier gave the update of "Project Lightning" relating that the "Project is now in development phase… UltraPro is the most promising available mesh for pelvic floor repair". Dr. Arlt from Berlin said that his experience with UltraPro in hernia surgery showed "almost no

problems like pain, shrinkage or recurrences…" A subsequent discussion was held "about the value of changing Prolene Soft to UltraPro". [97]

A small German company based in Aachen by the name of FEG also developed a PVDF surgical mesh implant, Dynamesh.

Evidently, despite the pathological animal test results from 2002 with Klosterhalfen, Ethicon had a renewed interest in trying to develop Pronova (PVDF) sutures as a pelvic floor mesh. As a result, they began a new project to investigate this PVDF PFR design concept through a new project dubbed by Ethicon as "Project Thunder".

A Project Thunder expert meeting was held in Leuven, Belgium, April 12, 2007, with Klosterhalfen, Deprest, Meier & Trzewik. Klosterhalfen states that the currently used material provides a good biocompatibility; no significant modification possible. Deprest feels that "Still problems to define the biomechanical boundary conditions" and the implant arms should be reduced or absorbable; and the probability of erosions is doubled in the area of incision related scar formation." [161]

Thunder Meeting Minutes dated April 12, 2007: Jonathan Meek "to take the lead on discussing legal activities against Dynamesh." Also states "IP protection of PRONOVA: Patent expired lately. New IP has to be filed on certain polymers on construction of implants." "More resources available for Thunder in Norderstedt (Textile experts) and at Boos. Local technician team formed….Samples for preclinical screening ready (first implantation Dec 13th)…Prosima and Prolift should be the first shapes tested with new Thunder material." [163]

June/July 2007: Clifford Volpe and Peter Meier emails and PowerPoint presentation "Exploratory Program 'Thunder' – A Material designed for the pelvic floor": "The Benchmark is Ultrapro" and a "**solid scientific basis** is needed regarding: 1. Biomechanics of the Pelvic floor; 2. Anatomy; 3. Causes of side effects of current procedures; 4. Test method refinement, diagnostics (e.g. Ultrasound)", p.2. "Worldwide Expert meeting in Lille [on Sept. 7, 2007] showed: We are at the front of scientific know how regarding PF [pelvic floor], but AMS & Tyco are coming." Also, "VoC at ICS revealed: True Elasticity is key, different mechanical properties needed within implant, less foreign material desired", p.3. [163]

July 31, 2007 Thunder Meeting Minutes – UltraPro is benchmark, intensify scientific work (pre-clinical, ultrasound, collagen inducing techniques). Discussion with Klosterhalfen re explants database; ultrasound experts - does 3D US result in data for scientific base of Thunder; Van Raalte (Lucente's fellow) trying to validate an instrument to measure vaginal elasticity transrectally – Dave sees no value in measuring vaginal skin parameters since that has been done and published. Holste performing a preclinical study of a collagen coated PP Mesh. [164]

August 14, 2007 Thunder Meeting Minutes – Ultra-light PP mesh ready, Pronova in process. Pros and cons of **Pronova to PP: Pro: Softness, Elasticity, better biocompatibility, less "aging" long time breakage, easier to manufacture and sterilize. Con: "May be more expansive (*sic*)".** Preclinical on collagen coated PP started – histology results expected late September [165]

Thunder Meeting Minutes December 18, 2007 – J questioned using of Prolift and Prosima as the first shots regarding the shape of Thunder – shapes have to be found that fit

anatomy better.; 3D Ultrasound is fascinating, dynamic means of evaluating meshes in vivo and shall be included into T. Activities. Status on raw material: Cornelia will produce PP filaments and R&D Somerville (I. Dris) PVDF copolymer for T. [119]

In February 2008, Ethicon held a meeting to discuss the "Thunder: Technical Review." [83] Under the heading "What is Thunder? Why Thunder is needed?" a few of the stated reasons are worth noting:

Page 4:

- "PF Repair market potential > 300 MM$";
- "No PF specific mesh on the market – Biomechanics of POP poorly understood > research needed";
- "Main unmet needs defined: Restore the natural anatomy and function of the pelvic floor & vagina; …Reduce shrinkage, dyspareunia, pain…Reduce amount of foreign material (over engineered)…Increase physiological in growth and elasticity of ingrown implant"

Page 5:

- "Strategy of Thunder – target: better patient outcome, competitive advantage; - approach: material that is more physiologically adapted to pelvic floor (getting closer to 'no mesh'); -conditions: …Thunder is a material development program: the material will go into a pelvic floor kit that is in development at the time of availability of Thunder; - other polymers than PP are conceivable, if they fit into the overall timing and have a measurable benefit."

Then, in May 2008, Ethicon prepared another PowerPoint presentation regarding Thunder. More interesting statements are found in those materials: [46]

Page 3:

- "Customer Feedback on PFR Devices – the majority of PFR surgeons are still not using kits";
- "There is still NO evidence of a Device created specifically for the female pelvis";
- "Potential Roles for Thunder – SO…The key is to focus on patient-centric transformational change…**1st Device specifically developed for Female Pelvic Floor**."
- **Stress shielding needed to avoid pore-collapse, deformation and pre-stretch**
- **Overview: Thunder options (Slide 7) – Is a grid comparing three potential mesh designs "T-Simple", "T-Pro" and "T-3" against Gynemesh and UltraPro. All three meshes rank higher than Gynemesh PS and Ultrapro for every attribute, except price.**

In a February 2007 PowerPoint presentation titled "Project Lightning Update", Ophelie Berthier, Marketing Manager EMEA described the new mesh material, Ultrapro as a partially absorbable, monofilament, large pore, pliable, vaginally compliant mesh with little memory. Ms. Berthier states that, in general surgery (hernia), Ultrapro had proven to cause less inflammation, induce less fibrosis, have better integration to host tissues, maintain the mobility of the abdominal wall, have an outstanding biocompatibility, and improve patients' quality of life. During the first cadaver lab of Project Lightning, Dr. Lobodasch found a significantly smaller amount of "curling" in the mesh arms after implantation, after the second cadaver lab, Ethicon's Key of Opinion Leader, Dr. Vince Lucente stated, "This one and throw the rest out…This feels like a piece of vaginal wall…"[161]

David B. Robinson, MD, Medical Director of Ethicon Women's Health and Urology, stated in his clinical expert report, "The use of Gynemesh PS (also referred to as Prolene Soft Mesh) for pelvic organ prolapse (POP) has been proven safe through a vaginal approach. Although it significantly reduced recurrences as compared to traditional repair, it can lead to other complications such as mesh exposure and mesh retraction. Mesh exposure is rather common…Mesh retraction "shrinkage" is a more uncommon complication but it is considered more serious. It can cause vagina anatomic distortion, which may eventually have a negative impact on sexual life…the scar place that forms with ingrowth of tissue into the mesh can cause stiffness…In an effort to minimize these complications, the use of an alternative mesh for pelvic organ prolapse repair was explored…" [166]

In March 2008, there was an email exchange between Dr. David Robinson and Dr. Vince Lucente regarding Ethicon and Lucente's interest in Lucente implanting Ultrapro (hernia mesh) as a PFR mesh in his patients. Robinson indicated to Lucente that he was trying to "get Regulatory to call this on-label use. I know it sounds ridiculous but at the moment, we are not seeking an indication for UP as a flat mesh. It raises all sorts of cost issues with Ethicon Products who obviously sells the same mesh for hernia… sorry something so simple seems so hard but I can tell you it is only going to get worse as the gov. interest shifts from pharma to device", to which Lucente responded, "…I'm in a VERY difficult position with the young patients that have been waiting for 'better' mesh for nearly one year. At the risk of being insensitive to corporate balance sheets… our patient's pelvic health and improving their outcomes with transvaginal mesh surgery should trump the profit margin issue." [167]

Prolift +M using Ultrapro mesh was launched and received 510(k) clearance in May 2008, four years after the developers of the TVM technique suggested a different mesh material for use in the Prolift kit and 10 years after Ethicon had learned through the research of myself and my colleagues of safer alternative mesh designs. Also, despite the stated design and complication advantages of Prolift +M over Prolift, Ethicon continues to market and sell what they have essentially claimed as an inferior device!

Pete Meier suggested to Dr. Hinoul, et al. in July 2009, that Pronova may be more elastic than polypropylene and show less degradation. [18]

A short Power Point presentation states that during the period from November 2010 to October 2011 Project Thunder was "killed" due to "tech push". [168] Although it is unclear as to what "tech push" infers, in multiple places, Ethicon seems to focus on the fact that PVDF costs more than PP. [46, 165] In their May 9, 2008 Thunder MGPP presentation, one slide is

particularly telling. It shows the PVDF products all out-performing Gynemesh PS and Ultrapro in ever design attribute EXCEPT cost. [46]

Cliff Volpe, the Associate Director of R&D testified in deposition that he was the sponsor of Project Thunder. As to the project, he testified: [169] "It was in exploratory for a while. I don't recall exactly. We initiated it into discovery for a while. We didn't initiate thunder itself, because it was just a material exploration. At some point, we initiated a discovery project to look at potentially putting the information from Project Thunder into the next generation for Prolift®, which would have been called T-PRO, thunder and Prolift®. Ultimately, at some point, we decided that -- to cancel that project… I don't think with our early – our early information for the technologies we were looking at, didn't seem to provide any additional benefit than Prolift+M® or the lightning project. So we decided to go back. We didn't really -- cancelling is probably a different -- we went back into exploratory with Project Thunder, so we decided that we needed to learn more and understand to make more improvements in Project Thunder, so… We looked at… the same fibers, you know, the Monocryl® and the polypropylene. And I believe we also looked at Pronova, which is another VDF [sic], I think is the chemical initials." "I would say it was an Ethicon recommendation -- it was accepted by the Ethicon leadership team [to use UltraPro] as a project to move forward."

Interestingly, in the PA Consulting report in May 2011, under the heading "Product development routes and concepts for consideration", it states "one theory is that the better the bio-stability of the material the lower the potential for mesh erosion – Pronova was suggested as a more stable material with the elastic properties required for pelvic floor repair mesh." It states that this theory and these observations were given by Prof. Klosterhalfen. [116]

7. SUMMARY OF OPINIONS:

Prior to launching Prolift for sale in the U.S., according to their own documents, Ethicon was aware of the following design requirements for a safe pelvic floor mesh product:

- Recreate and maintain the physical characteristics of the vaginal wall;
- Mimic the human tissue mechanical properties;
- Have elastic properties that match the hyperelastic properties of the vagina;
- Have multi-directional stretchability which easily conforms to the tissues surrounding the vaginal wall;
- Remain pliable as a result of pelvic organ filling/emptying, pelvic tissue pliability and sexual function;
- Incorporate into surrounding tissues;
- Not shrink or contract;
- Lightweight material;
- Strength of the material needs to be equivalent to the strength requirements of pelvic floor muscles/tissues (i.e., the prosthetic must not be "over-engineered")
- Have pore size > 1mm in all directions;
- Avoid pore collapse and pore deformation under strain;
- Have good "memory" after stretching;

- Resist “curling” or “roping”, especially in the mesh arms, after implantation;
- Edges must be smooth not frayed and sharp;
- Be histologically well tolerated (inert);
- Not degrade;
- Resist infection; and,
- Be easily handled and implanted.

[7, 16, 23, 28, 29, 34, 41, 44, 46, 47, 48, 95, 97, 122, 151, 163, 167, 168]

According to their documents, Ethicon also knew why these design requirements were so important in terms of patient safety:

- Mesh that mimics the compliance of the supported tissue results in more comfort and function after implantation;
- Biomechanical compliance of prosthetic meshes to soft tissue reduces the FBR;
- Large pore size (> 1mm) leads to better handling properties and better ability of the mesh to interact with the tissues in which it is implanted; allows for swift and adequate tissue ingrowth; minimizes FBR and wound contraction; causes less fibrotic bridging and “scar plates”;
- Less FBR, inflammatory reaction and wound contraction is associated with less shrinkage/contraction;
- Pore size is a crucial measure for the safety and efficacy of mesh implants;
- If pore size/geometry deforms under minimal stress/force, this will affect the safety and efficacy of the mesh implant;
- Lighter weight material with large pores leads to less shrinkage;
- Shrinkage leads to increased stiffness of the mesh, pain and poor restoration of the normal properties of the vagina;
- Shrinkage leads to vaginal anatomic distortion which may eventually have a negative impact on sexual function;
- Strong fibrosis almost always leads to wrinkle formation in the mesh due to increased shrinkage;
- Shrinkage and wrinkle formation are associated almost always with erosions;
- Small > medium pore meshes and medium > light weight meshes precipitate a strong FBR and fibrotic scarring/bridging;
- Infection is commonly observed following erosion in the vaginal mucosa;
- Inflammation with fibrosis leading to mechanical irritation is one of the primary causes of mesh-induced erosion and ulceration;
- The larger the pore size the less the risk of erosion;
- Infection is a predisposing factor for mesh erosion;
- Frayed edges lead to excessive inflammatory reaction;
- Severe FBR = Severe fibrosis = Degenerative calcification around mesh fibers;

[29, 103, 122, 123, 150, 151, 152]

However, as is also stated in their documents, Ethicon was aware of the challenges and uncertainties of designing a safe mesh for the pelvic floor; that the design of Prolift did not meet all their claimed optimal design requirements; and that as a result, this led to patient complaints and complications:

- "The ideal mesh for prolapse repair which mimics precisely the biomechanical needs of the pelvic floor region has not been developed";
- "There is significant evidence that the complications associated with synthetic meshes can cause significant morbidity including infection, erosion, exposure and pain";
- "There is evidence that meshes shrink in vivo leading to increased stiffness, pain and poor restoration of the normal properties of the vagina";
- "There is no descriptive model available to predict the mechanical behavior of pelvic mesh implants";
- "The [TVM] group is strongly looking forward to a potential for materials for the Prolift product. Their main concern is the[y] believe that the Prolene Soft material over time contracts. Thus creating the potential for failures and/or erosions";
- "This mesh [the Gynemesh PS used in Prolift] was not 'specifically designed' for Prolift application; we pulled the mesh out of our existing bag of tricks";
- "Material science has been slow to meet the special requirements of the vaginal environment";
- "The vagina is not the abdomen and it is not similar to any other surgical environment";
- "The pelvis has a complex, 3-dimensional architecture and vector forces with little or no bony (and often pelvic floor muscle) reinforcement";
- "Polypropylene is the best of a bad lot re integration and contraction and there is a need to develop grafts that mimic the human tissue mechanical properties"
- "The development of knowledge to understand the mechanics of pelvic floor disorders is imperative; yet, we are only just beginning to determine the necessary criteria on which to base design for pelvic floor implants";
- "In fact, many meshes may be over-engineered with respect to strength and mesh density and weight may be able to be significantly decreased. However, the extent of this decrease and the minimum mesh strength requirement for pelvic floor repair is not known";
- "Pelvic floor materials are still over-engineered";
- "There is no patient-centric pelvic floor material";
- "We need less foreign body material and materials that correlate to measured female pelvic physiological characteristics";
- "We have no idea what pelvic floor pressures are";
- "There is still NO evidence of a Device created specifically for the female pelvis";
- "[We need a] unique and proprietary material (it cannot be what we currently know as Mesh)";
- "Most of the information dealing with the biomechanical behavior of the soft tissues involved in the pelvis are presented in the literature with very [little] information on the material compliance";

- "[There is] almost no information [in the scientific literature] dealing with the mechanical behavior of the other involved tissues (rectum, bladder, uterus, ligaments, and muscles)";
- "In pelvic floor surgery, shrinkage seems to be more important than in hernia surgery";
- "Polypropylene meshes might not be improvable in terms of shrinkage; we may need a completely new material";

[7, 28, 29, 31, 33, 39, 41, 46, 47, 48, 97, 162]

Ethicon has a long history of manufacturing surgical meshes that are intended to be permanently implanted by doctors in patients' bodies. They likewise have a long history of reported complications with their prosthetic meshes. With their experience from complications associated with some of the poor design characteristics in hernia meshes, Ethicon was on notice that poor design leads to poor outcome. Also from that experience, Ethicon should have learned that when they properly addressed and modified certain characteristics of the mesh to ensure that they were biocompatible and biomechanically adapted to the tissue in which they would be expected to function, patients benefitted with better outcomes. Conversely, Ethicon should have learned that when they choose NOT to properly design and test their products to address design-related complications, it can have disastrous results.

Through my team's collaborative efforts with Ethicon in the late 1990's and early 2000's, Ethicon learned that the development of an optimal surgical mesh design for any application has to consider first, the polymer; second, the biomechanics (physiological requirements) as to strength, elasticity and structural stability; and third, the structure of the device in terms of geometric design, knitting characteristics, fiber size and pore size. Ethicon knew that the result of these design considerations and choices would influence the tissue reaction, primarily the intensity of the inflammatory and fibrotic response, thereby directly affecting the biocompatibility of the device and thus the clinical outcome regarding potential complications such as chronic infection, chronic pain, erosion, shrinkage, dyspareunia, migration and recurrence. However, despite this knowledge, Ethicon failed to appropriately design and test its pelvic mesh kit, Prolift to determine if these unintended and adverse events would occur when implanting Gynemesh PS permanently into a woman's pelvic tissues. As a result of these failures, Ethicon more likely than not caused injury to women in the United States and around the world.

Ethicon was required to do more than to simply prove that Prolift would restore anatomy and function. Those outcomes are merely anatomic and are not necessarily related to the most important characteristic of any surgical procedure: Is the patient's health improved and is their quality of life better? Because even if Prolift is successful, on the one hand, by holding the pelvic organs in place, it is a disastrous failure if it leads to long-term serious complications like erosions, chronic pain, permanent sexual dysfunction, chronic wound healing issues and chronic infections.

Of course, as we have seen, Prolift's design has led to an increased occurrence of all of these complications and more. As such, it is not a safe product and the risk of Prolift far outweighs any claimed benefit.

As I mentioned earlier in this report, unlike my work with Ethicon in quantifying the physiological forces that are placed on the tissues in the abdominal wall and constructing a prosthetic mesh that adapts to those characteristics, it appears that Ethicon never earnestly attempted, much less, successfully conducted, similar studies, animal or otherwise, in constructing new generation pelvic meshes. To the contrary, apparently Ethicon merely referenced our work on new generation hernia meshes as a basis for making claims regarding their revolutionary, specially-designed, pelvic floor mesh while simultaneously failing to incorporate our design changes and considerations. This failure and flawed design process has proven dangerously faulty as injuries to numerous patients continue to mount.

Again, the most prudent course of action by Ethicon following the development of Vypro would have been to continue to utilize the newly-developed design characteristics that reduced complications in hernia mesh patients and to then design tests and pre-clinical studies that applied specifically to pelvic floor meshes in order to develop better and safer design characteristics that would reduce complications in pelvic mesh patients. Instead, what Ethicon did was to use the general findings from these early hernia studies to unreasonably justify their later claims in submissions to FDA and in IFUs to surgeons that the various iterations of their pelvic mesh products demonstrated the same characteristics of physiological tissue adaptation in the pelvis and were thus safely designed. Such an approach by Ethicon was faulty on many levels, all of which were poorly considered and led to an increased risk of injury to patients.

Ethicon has stated repeatedly in its documents that it had a very poor understanding of the biomechanics of the pelvic floor which apparently continues to this day. The problem is, of course, if the manufacturer of a permanently-implanted, synthetic device does not have a sufficient understanding of the biomechanical properties of the tissue in which the device will be implanted, nor an adequate understanding of the biomechanical forces of the area of the body in which the device will be implanted, it is impossible to establish reliable parameters for the design of the device. Accordingly, the risk of short- and long-term complications to the patient are dangerously increased, thereby exposing patients to injury, and the product cannot and should not be placed on the market. This was certainly the case with Prolift.

With the development of Vypro, the first truly large pore mesh, we were able to increase the pore size by up to 500-600% (Vypro 3-5 mm vs. Prolene <1mm). Given that the risk of bridging fibrosis is increased by mesh with pore size < 1mm in all directions, any mesh designed with pores this small increases the risk of injury to the patient and is a less safe design than mesh with pore sizes > 1mm in all directions. Simply put: the greater the pore size or open space in between fibers, the less the risk of fibrotic bridging and formation of a rigid and potentially dangerous scar plate encapsulating the mesh and igniting the cascade of untoward subsequent events following this intense inflammatory/fibrotic process. Ethicon had this information beginning in 1998, but ignored it in their design of Prolift.

The significance of the Muhl method of testing these mesh products is that it provided useful data in terms of how the mesh, and different parts of the mesh, will perform in the human body. The first most important observation from this testing was that the effective porosity and the effective porosity under strain seen with Prolift produced results which demonstrated its likely unsafe performance in the human body. As minimal strain was applied to the test samples, the geometric shape of the pores deformed and ultimately collapsed. This deformation led to

extremely small pores which would make the mesh highly susceptible to fibrotic bridging, encapsulation by a rigid scar plate and the array of potential complications that occur as a result of this inflammatory process as mentioned in previous paragraphs.

Furthermore, despite Ethicon's apparent knowledge of the significant amount of mesh shrinkage experienced by patients in whom Prolift had been implanted, the potential causes of mesh shrinkage, as well the resultant patient complications that could occur as a result of said shrinkage, they did no testing nor made any design changes to Prolift in order to reduce the occurrence of this known and serious complication. Failure by Ethicon to properly study and/or make the necessary design changes to avoid this and the other safety hazards mentioned in this report was improper, irresponsible and threatened patient safety.

The design of the Prolift device creates an unreasonable risk of the following complications:

- Erosion/exposure/migration due to FBR and inflammatory response;
- Chronic Pain due to FBR, inflammatory response and shrinkage;
  - Nerve Damage/Entrapment
  - Dyspareunia/Sexual Dysfunction;
- Infection due to bacterial adherence, FBR, chronic wound healing and biofilm;
- Recurrence due to FBR, inflammatory response and shrinkage; and,
- Urinary Complications due to dysfunction with obstruction or incontinence because of secondary scarring and shrinkage.

The Prolift has serious design deficiencies that exist even with warnings, in the most highly-skilled surgeons' hands and with the most properly selected patient, the product still presents a dangerously increased risk of patient injury.

On June 5, 2012, seven years after the Prolift was made available for sale, the New York Times reported [170] that Ethicon has advised the FDA that it will withdraw the Prolift from the market. For the reasons set forth throughout this report, Ethicon should have never marketed and sold the defective Prolift system in the first place.

More likely than not, the Prolift® has caused numerous complications/injuries, as described in this report, as a result of this product and procedure.

I reserve the right to modify these opinions as necessary based upon any new or additional information or data that I may obtain or with which I am presented.

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APPENDIX A

CV Professor Dr. med. Uwe Klinge

Born at 30.4.1959 in Wilhelmshaven, Germany

Primary, secondary, high school	1964-1977 Wilhelmshaven
Medical school	1977-1983 RWTH Aachen

Medical profession

12/1983 – 2/85:	military service VKK 321, Düsseldorf
1.3.1985:	surgical resident ship at the Surgical Department of the University Hospital at the RWTH Aachen (Head Prof. Reifferscheidt, after 12/85 Prof. Schumpelick, after 3/2010 Prof. Neumann)
1992:	Thesis at the Department for biochemistry, Prof. Gersonde at 29.4.1985 „In-vitro investigation of the oxygen binding curve of human erythrocytes in the presence of glucose and insulin “
15.12.1993:	Specialist for general surgery
seit 15.10.1999:	Oberarzt of the surgical Department
1/2000	Venia legendi for Surgery, Habilitation with the title „Use of alloplastic meshes for the repair of abdominal wall hernia: optimisation by adjustment to the physiological requirements “
seit 15.10.2000:	Principal investigator of the surgical department
21.3.2002:	specialist for surgical intensive care medicine
1.1.2003 – 1.11.2006:	Assistant medical director
21.7.2004:	Specialist for visceral surgery
13.12.2005:	appointment as a.pl. Profess
1.11.2006-28.2.2009:	Cooperation with the Institute for applied medical engineering of the Helmholtz institute

Scientific work

- Pathophysiology and treatment of abdominal wall hernia
- Biomaterials and tissue response
- Impact of altered ECM for wound healing and cancer development
- Analysis of biological networks
- Identification of prognostic markers
- Optimisation of staplers

Publications

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174. U. Klinge: Die Chirurgie der Leistenhernie – von der Stange oder nach Maß? Fortbildungsveranstaltung der AEKNO, Kreisstelle Duisburg 20.2.2008

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176. U. Klinge: Welche Hernie braucht ein Mesh? 1. Tagung der Schweitzer Herniengesellschaft in Bern, 4.4.2008
177. U. Klinge: Welche Probleme können bei der Verwendung von Netzen in der Hernienchirurgie auftreten? 125. Kongress der DGfC, 22.-25.4.2008, Berlin
178. U. Klinge : Low-weight polypropylene mesh: what is the clinical importance of the porosity
for hernia repair? 30. congreß of the EHS, Sevilla, Spain: 7-10.5.2008
179. U. Klinge: Grundlagen der Hernienreparation aus Sicht des wissenschaftlichen Chirurgen. 5. Tagung der Deutschen Hernien-Gesellschaft, Baden-Baden:29.-31.5.2008
180. U. Klinge: Postoperative CRPS in inguinal hernia patients. 5. Suvretta-Workshop, St. Moritz: 1.-7.7.2008
181. U. Klinge: Two controversial concepts: Standard procedure in a standard patient versus
tailored surgery with procedures adjusted to individual patients? 5. Suvretta-Workshop, St. Moritz: 1.-7.7.2008
182. U. Klinge: Degradationsprozesse und Netzbrüche in der Hernienchirurgie. 3. Wilhelmsburger Hernientage, Hamburg: 5.-6.9.2008
183. U. Klinge: Update Biomaterialien und Netze in der Hernienchirurgie. 12. chir. Forschungstage, Freiburg: 25.7.-29.9.2008
184. U. Klinge: Classification of incisional hernia - from Aachen‘s point of view. Consensus meeting on the development of an EHS classification, Gent, Belgium, October 2nd - 4th 2008
185. U. Klinge: What should be considered for selection of mesh material. AHS, Beijing, 1.-2.11.2008
186. U. Klinge: The CRPS after groin hernia repair. AHS, Beijing, 1.-2.11.2008
187. U. Klinge: Hernia repair tailored to the patient instead of using a gold standard?. AHS, Beijing, 1.-2.11.2008
188. U. Klinge: Future perspectives in textile implants. AHS, Beijing, 1.-2.11.2008
189. U. Klinge: Update mesh. Shanghai. 28.11.2008

190. U. Klinge: Hernia and Collagen. 4. Rotterdam interactive congress for hernia, 21.11.2008, Rotterdam, NL
191. U. Klinge: Was ist bei der Auswahl von Meshes zu beachten? Zürser Hernienforum 14.12.-16.12.2008, Zürs, Austria
192. nicht mehr aktualisiert
193. U. Klinge, N. Farthmann, A. Fiebler: Aldosterone network. San Diego, 17.6.2010
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Oral presentation on invitation:

1. U.Klinge Review of literature and experimental results of mesh surgery Expert-Meeting Suffretta-House St. Moritz Feb. 1994
2. U.Klinge Pathophysiologie der Narbenhernie Chirurgentag Nürnberg 24.10.1996
3. Conze, J., U Klinge (1998) Biocompatibility of biomaterials – clinical and mechanical aspects. II Suvretta meeting: abdominal wall: function, defects and repair. 8.-14.3.1998 St. Moritz Swiss
4. U. Klinge, B Klosterhalfen (1998) Biocompatibility of biomaterials – experimental aspects. II Suvretta meeting: abdominal wall: function, defects and repair. 8.-14.3.1998 St. Moritz Swiss
5. B. Klosterhalfen, U. Klinge (1998) Biocompatibility of biomaterials – histological aspects. II Suvretta meeting: abdominal wall: function, defects and repair. 8.-14.3.1998 St. Moritz Swiss
6. U. Klinge (1998) Meshes zur Hernienreparation. 7. Interdisziplinäres Forum der Förderation operativer medizinisch-wissenschaftlicher Fachgesellschaften 17.10.1998 Wiesbaden
7. U. Klinge (1999) Chirurgie der Narbenhernie. 5. Kölner Tagung ambulantes Operieren. Köln, 7.5.1999
8. U. Klinge (1999) Pathophysiologie der Bauchdecke. Weißenseer Operationskurs 24.9.99
9. U. Klinge (1999) Rezidive und Patientenkomfort im Langzeitverlauf. Weißenseer Operationskurs 24.9.99
10. U. Klinge (7.12.1999) Meshes in der Hernienchirurgie. 5. Zürser Hernienforum, Zürs, Austria
11. U. Klinge (9.3.2000) Narbenhernienchirurgie: Primärverschluß oder Netzimplantat? Interdisziplinäre Viszeralchirurgie am Inselspital, Bern, Schweiz
12. U. Klinge (3.5.2000) Biomaterialien in der Hernienchirurgie. FomwF, 117. Kongreß der Deutschen Gesellschaft für Chirurgie 2.-6.5.2000, Berlin
13. U. Klinge (4.5.2000) Epidemiologie und Pathophysiologie der Bauchwanddefekte. Narbenhernie, 117. Kongreß der Deutschen Gesellschaft für Chirurgie 2.-6.5.2000, Berlin
14. U. Klinge (26.5.2000) Anatomy and physiology of the abdominal wall. Laparoscopic incisional hernia repair a standard therapy? Rastatt, 25.5-27.5.2000

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19. U. Klinge (2000) Netzimplantate in der Hernienchirurgie – Charakteristika und Anforderungen.Netzimplantate 22.-23.9.2000, Würzburg
20. U. Klinge (2000) Minimierte Polypropylen-Netze zur präperitonealen Netzplastik – prospektive Studie. 22.-23.9.2000, Würzburg
21. U. Klinge (2000) Implantierbare Netze in der Chirurgie – Nutzen oder Risiko? Fortbildungsveranstaltung der Kreisstelle Mülheim/Ruhr 10.10.2000, Evang. Krankenhaus Mülheim a. d. Ruhr
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25. Klinge, U (2001) Rezidivoperationen und Biomaterial. 1668. Jahrestagung der Vereinigung Niederrheinsich-Westfälischer Chirurgen, 27.-29.9.2001 Bielefeld
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33. Klinge, U (2002) Impact of mesh material on clinical results. III Spotkanie Polskiego Klubo Przepuklinowego 20.-21.9.2002, Bydgoszczy, Poland
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42. Klinge U (2004) Pathophysiology and therapeutic impact of meshes. Utrecht 13.9.2004
43. Klinge U (2004) Biomaterials for Hernia repair. Utrecht 13.9.2004
44. Klinge U (2004) Standardoperationen – unterer GI-Trakt. Workshop Praktische Onkologie, Bonn 23.-24.10.2004

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50. Klinge, U (2005) Open-Non-Mesh: Shouldice – the good old way. 16.2.2005 Leistenhernienchirurgie 2005, Bethlehem-Krankenhaus, Stolberg
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64. Klinge U Recurrence as a problem of biology & collagens. 2nd Congress of the Asia pacific hernia society 2006, 6-8th October
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66. U. Klinge Standardoperationen bei Tumoren des oberen GI-Traktes. Inderdisziplinärer Workshop GI Tumore. 20-12.10.2006, Bonn
67. Klinge U. Meshes in der Chirurgie. Berlin 4.11.2006 Uro-gynäkologische Tage
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75. U. Klinge Meshes in der Chirurgie, Hamburg ESI Mesh-Forum 17.9.2007
76. U. Klinge Update Hernienchirurgie, Freiburg, 8.10.2007
77. U. Klinge: Does material and porosity of meshes matter? 8th congress of the panhellenic surgical society of northern Greece, 18-21.10.2007, Thessaloniki
78. U. Klinge: Concept of CRPS in the groin, and strategies for treatment. Pain & Hernia surgery symposium, ESI, Hamburg, 30th October 2007
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81. U. Klinge: Was können Goldstandards leisten? 14.12.2007 Berlin, http://www.gcp-workshop.de/1331.html
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tailored surgery with procedures adjusted to individual patients? 5. Suvretta-Workshop, St. Moritz: 1.-7.7.2008
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99. U. Klinge: Hernia repair tailored to the patient instead of using a gold standard?. 4th International Congress of the Asia-Pacifric Hernia Society, 5th Annual Conference of China hernia Society, 30.10.-2.11.2008, Beijing
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107. U Klinge: Welche Netze für die offene/laparoskopische Narbenhernienreparation ?. 30.4.2009 München, Jahreskongreß der DGFC
108. U. Klinge: Biomechanische Anforderungen:Was sollen und können Netze leisten ? 30.1.2009, Berlin 3-Chirurgen
109. U. Klinge: What has to be considered for selection of alloplastic nets and slings at the pelvic floor? 28.3.2009, Dijon
110. U. Klinge: Leuven Aachen Rotterdam Herniosis Studygroup LARHS 10.4.2009, Leuven

111. U. Klinge. Biologicals für die Hernienchirurgie? Jahreskongreß der Deutschen Herniengesellschaft in Neuss, 19-20.6.2009
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113. U. Klinge: Das ideale Mesh? Euregio Bodensee, 3.7.2009 St. Gallen
114. U.Klinge: Limitation and peerspective of Biologicals. Leeds, 23.10.2009
115. U.Klinge: Update Narbenhernienchirurgie unter Einbeziehung von Grundlagen der Netzstabilität. Chirurgische Abteilung, Uniklinik Essen, 26.10.2009
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119. U. Klinge: Textile structures fort he pelvic floor. Kopenhagen, 27.11.2009
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122. U. Klinge: Große Datenmengen für die Medizin? Arbeitstreffen E-Health, RWTH-Aachen, 25.1.2010
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127. U. Klinge: mesh classification? Dubai 2010
128. U. Klinge: Meshes für die Chirurgie. Fulda, EKK 17.5.2010
129. U. Klinge: Hernie - Gibt es eine einfache „Pathophysiologie“ München 11.6.2010 Deutsche Henriengesellschaft
130. U.Klinge: Wie kann man Meshes klassifizieren? BvMed 2.7.2010
131. not longer acutalised ….

Grants

Nr. des Teilvorhabens bzw. Name bei Neuprojekten	Projektleiter/ Mitarbeiter aus dem Zentrum	Thema des Drittmittelprojektes	Zuwendungsgeber/Aktenzeichen/Laufzeit	Zeit-raum	Umfang der Fördermittel in (DM) oder Stellen
	Klinge, Höer	Panacryl-Fadenstudie	Ethicon / 3 Jahre	1999-2002	260.000
	Klinge, Welty	Internationale Vypro-Studie	Ethicon / 3 Jahre	1999-2002	54.000
	Klinge, Welty	SHM-Studie	Ethicon / 2 Jahre	1997-1999	262.000
	Klinge	Kollagen-Studie	Ethicon / ½ Jahr	1999	30.000
TV 9	Klinge	Verwendung von Biomaterialien beim Bauchdeckenverschluß	BIOMAT 4 Jahre	1995-1998	208.107
TV 41/42	Klinge/Steinau	PVDF-Mesh	BIOMAT 2 Jahre Nachfolgeprojekt 2 Jahre	1999-2000 2001-2002	347.940
	Klinge	Mesh-Entwicklung	Ethicon	2000-2003	375.000 Kostenstelle: 9876170 Anforderungsnr.: 98761770
TV 66	Mertens, Klinge	Mesh-Fibroblasten	BIOMAT	2001-2002	330.000
TV 61	Bertram, Tietze, Klinge	Kokulturen	BIOMAT	2001-2002	210.000
FEG/BMBF	Klinge, Klosterhalfen	Entwicklung von neuartigen bioverträglichen Netzmaterialien zur anatomisch angepaßten chirurgischen Hernientherapie - Beschichtete Meshes	03N4024 FEG-065/1-2001	1.3-2001-2004	358.824,-
DFG	Klinge, Klosterhalfen, Mertens	Kollagen und Hernie	KL 1320/2-1	21.6.2001-21.6.2003	350.000,-
Ethicon	Schumpelick, Klinge, Stumpf, Junge, Schachtrupp, Steinau, Schwab	Optimierung von Mesh-Strukturen	370253	1.4.2003-31.3.2006	360.000 €
DFG	Lynen-Jansen Mertens Klinge Jansen	**Einfluß von Biomaterialien auf die MMP-2 Genexpression *in vivo***	DFG JA1123/1-1	2004-2005	120.000 Euro
DFG-Projekt	Lynen-Jansen Mertens Klinge Jansen ,	**Untersuchungen zur Gewebe-Integration von Biomaterialien bei selektiver Blockade der TNFα-abhängigen MMP-2**	DFG JA 1123/1-2,	Laufzeit 2 Jahre, Umfang Start 2008	ca. 120.000 Euro,

Nr. des Teilvor-habens bzw. Name bei Neupro-jekten	Projektleiter/ Mitarbeiter aus dem Zentrum	Thema des Drittmittelprojektes	Zuwendungs-geber/Akten-zeichen/Lauf-zeit	Zeit-raum	Umfang der Fördermittel in (DM) oder Stellen
		Expression'			
INNONET	HIA und Frauenhofer	**Die sichere Naht**	VDI/VDE	2/2008-2011	Gesamtvolume n 1,1 Mill €
Mesh insight	FEG und UK-Aachen Klinge U, Otto J, Krämer N, Obolenski B:	Sichtbarmachung von textilen Implantaten im MRT durch Einlagerung von superparamagnetischen Eisenoxid-Nanopartikeln. Innovationswettbewerb 2007 des BmbF zur Förderung der Medizintechnik, 18.10.2007	BMBF 01EZ0849	1.4.2008-31.1.2011. 3.2008-1.2.2011	Gesamtvolume n ca. 900.000€
	Kämmer, Otto, Klinge	PVDF-Mesh Beschichtung mit NN-Hormonen	ESAC	2008	12 000€
Bioinside	FEG/Fiebeler/B erlin	Beschichtung mit DHEA	BMBF BioInside 13N9827-13N9833 PN 372552	2008-2010	70 000€
	Klinge	InnoMeT.NRW: Patientenadaptierte Medizintechnische Lösungen für die Kardiovaskuläre Therapie	005-1003-0067 IAN 700584	1.8.2010-31.7.2013	270 000
	Klinge	Elastisches Netz-Implantat für die Chirurgie am Zwerchfell (Hiatus-Mesh)	ZIM-Projekt KF2621701AJ0	14.4.2010-31.10.2011	110 000€
	Klinge/Tolba	Covidien Stapler	372708	1.2.2010-31.1.2011	

Patents:

02754251.3-2107-DE0202287 FEG Textiltechnik vom 25.6.02: Textiles Implantat mit monofilen Polyvinylidenfluorid-Fäden

„Einstückiges Stomaunterstützungsimplantat“ WO 2008/031411 A1

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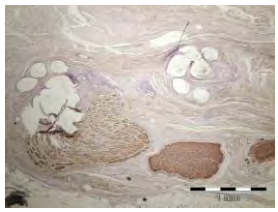
„Textiles Implantat“ WO PCT/DE02/02287

Editorial board

Editorial Board of World Journal of Gastrointestinal Surgery (WJGS)

APPENDIX B

FIGURE 1



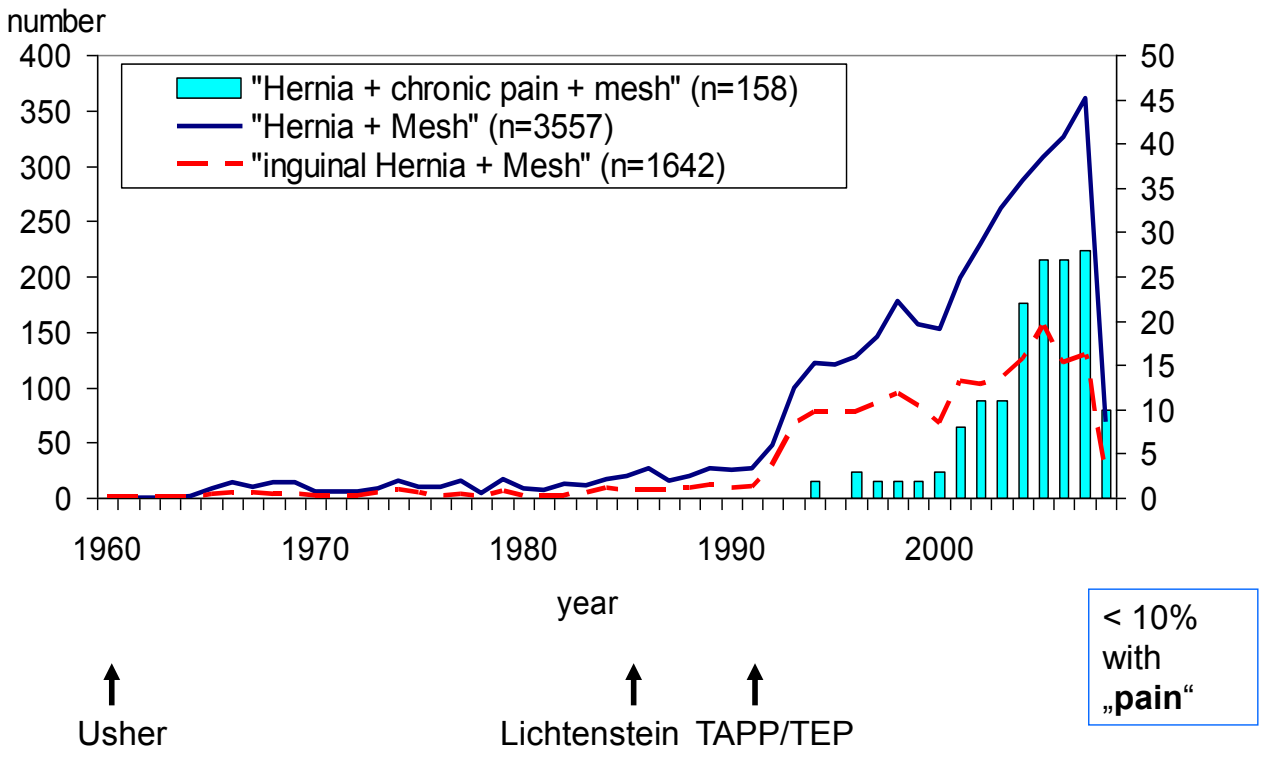

Delayed complications after mesh
publications in PubMed 1960-2008
number
400
350
300
250
200
150
100
50
0
50
45
40
35
30
25
20
15
10
5
0
"Hernia + chronic pain + mesh" (n=158)
"Hernia + Mesh" (n=3557)
"inguinal Hernia + Mesh" (n=1642)
1960
1970
1980
1990
2000
year
< 10% with „pain“
Usher
Lichtenstein
TAPP/TEP

FIGURE 2

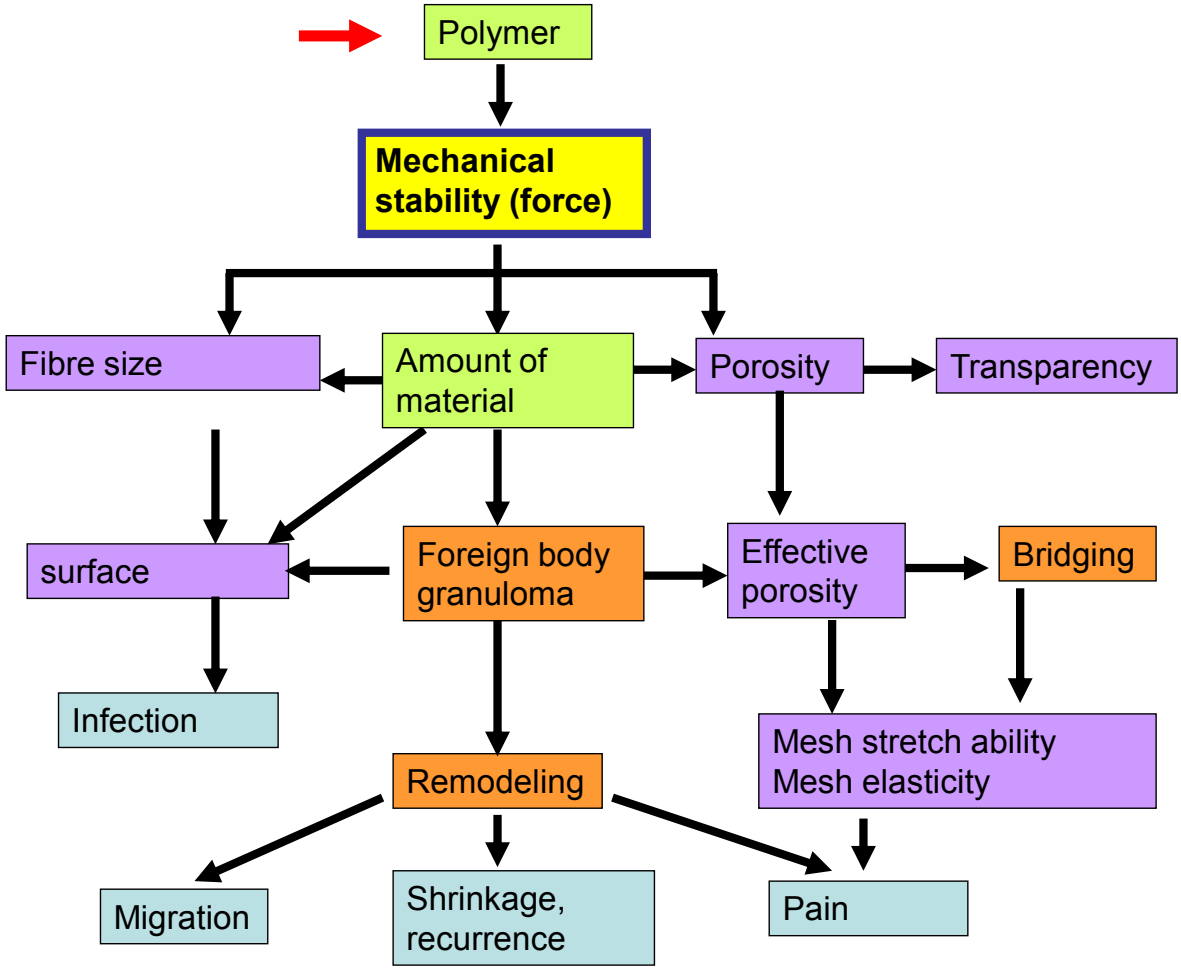
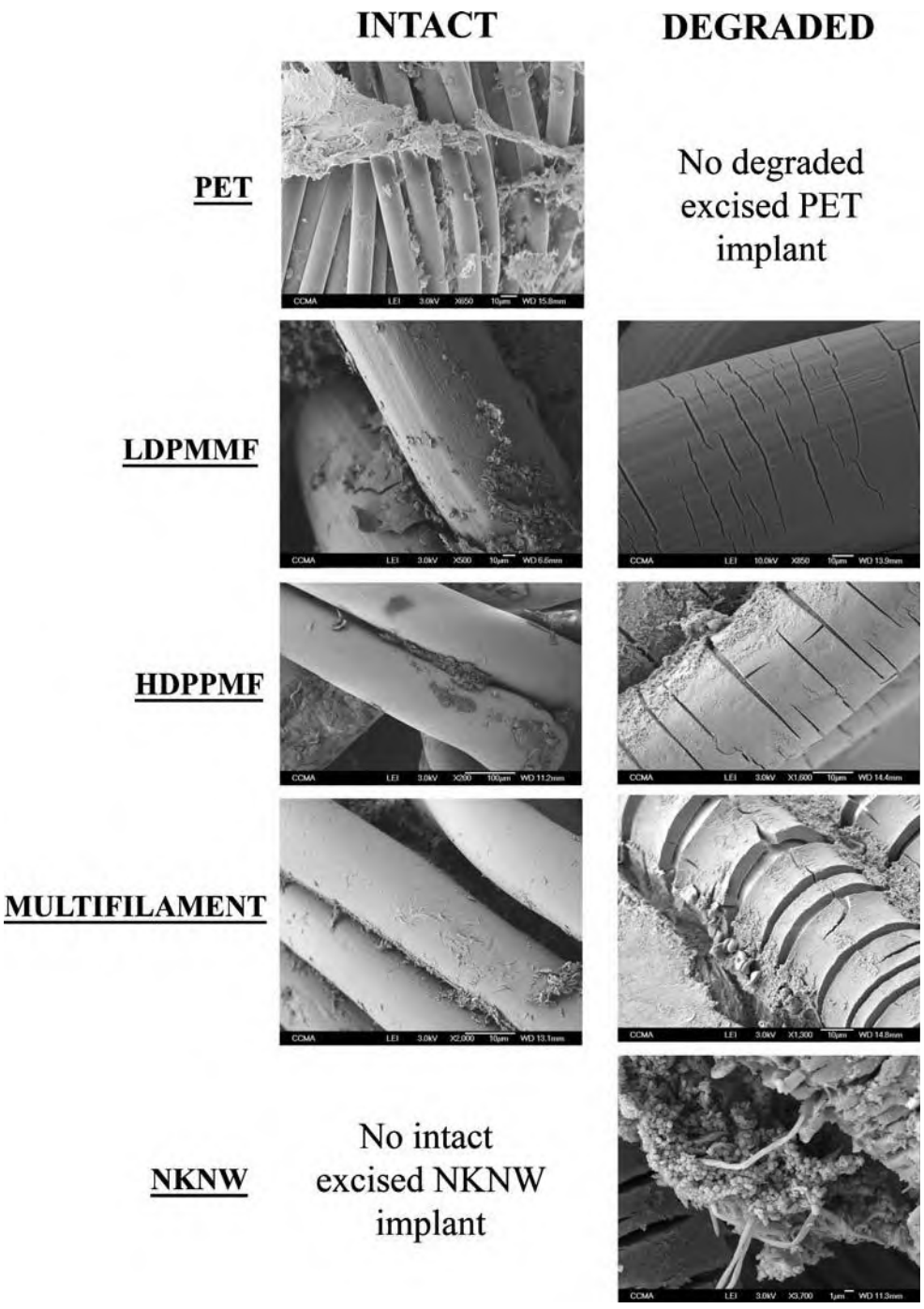


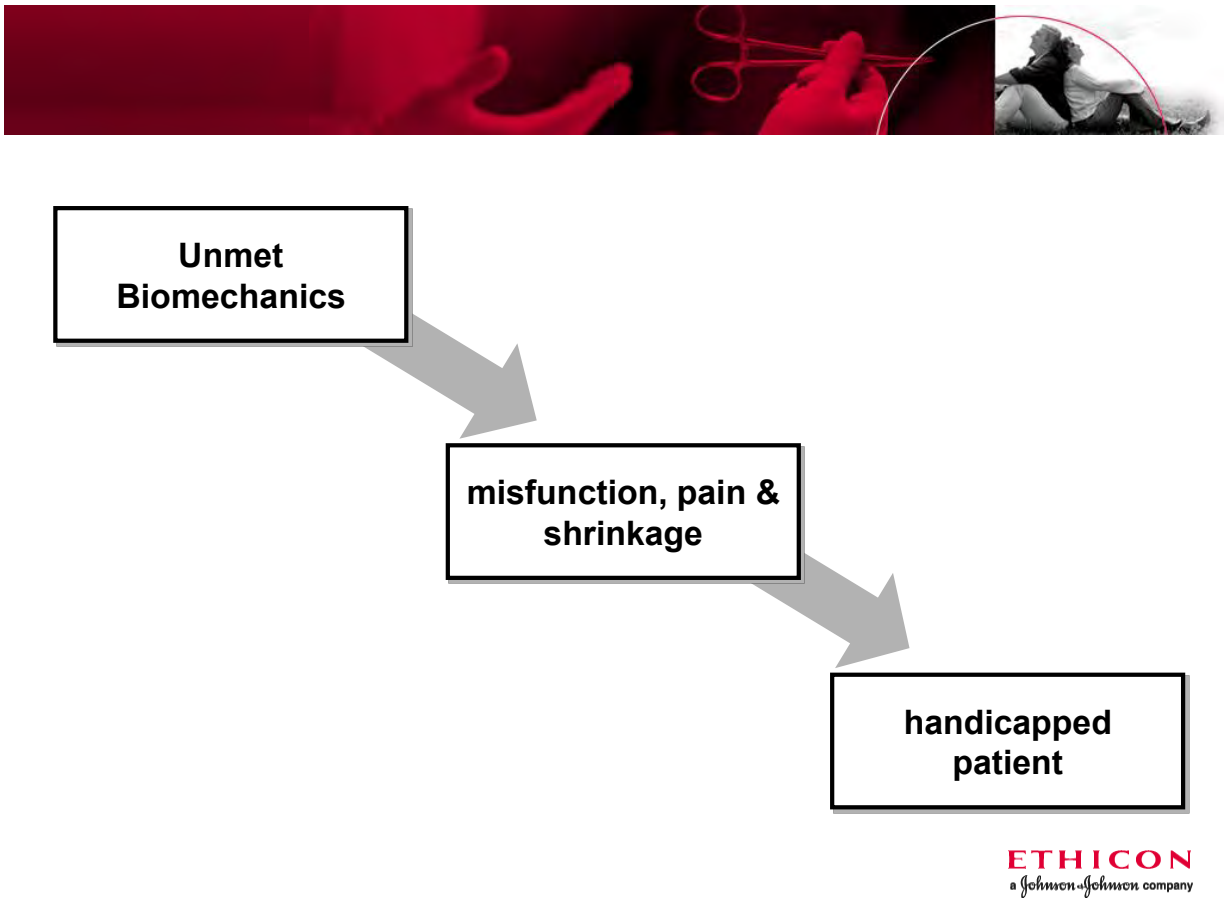
Fig.3: collaborative network of mesh

Figure 3



Int Urogynecol J (2010) 21:261–270

Figure 4



ETH.MESH.03753245: "Biomechanics" PowerPoint

Figure 5

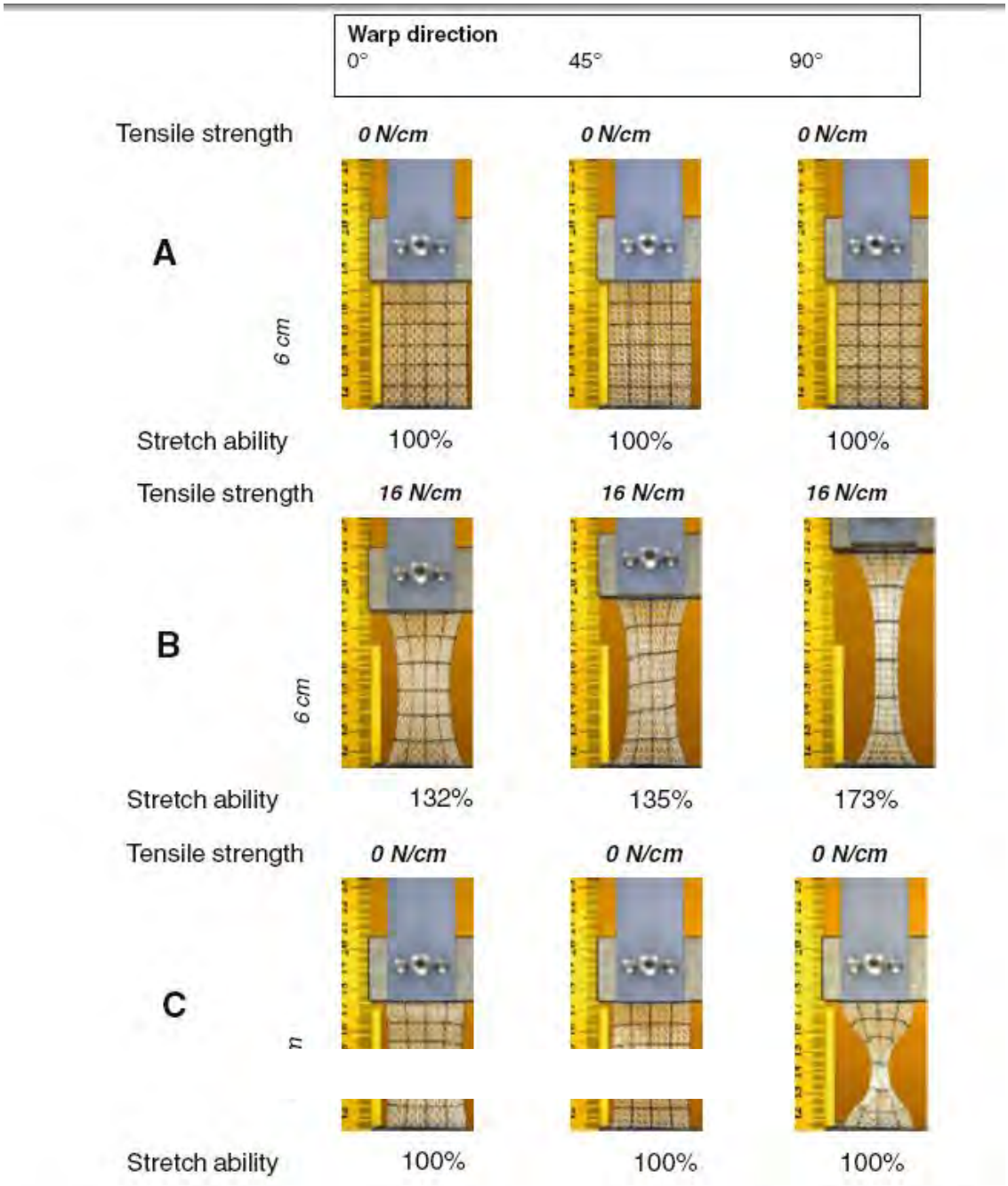
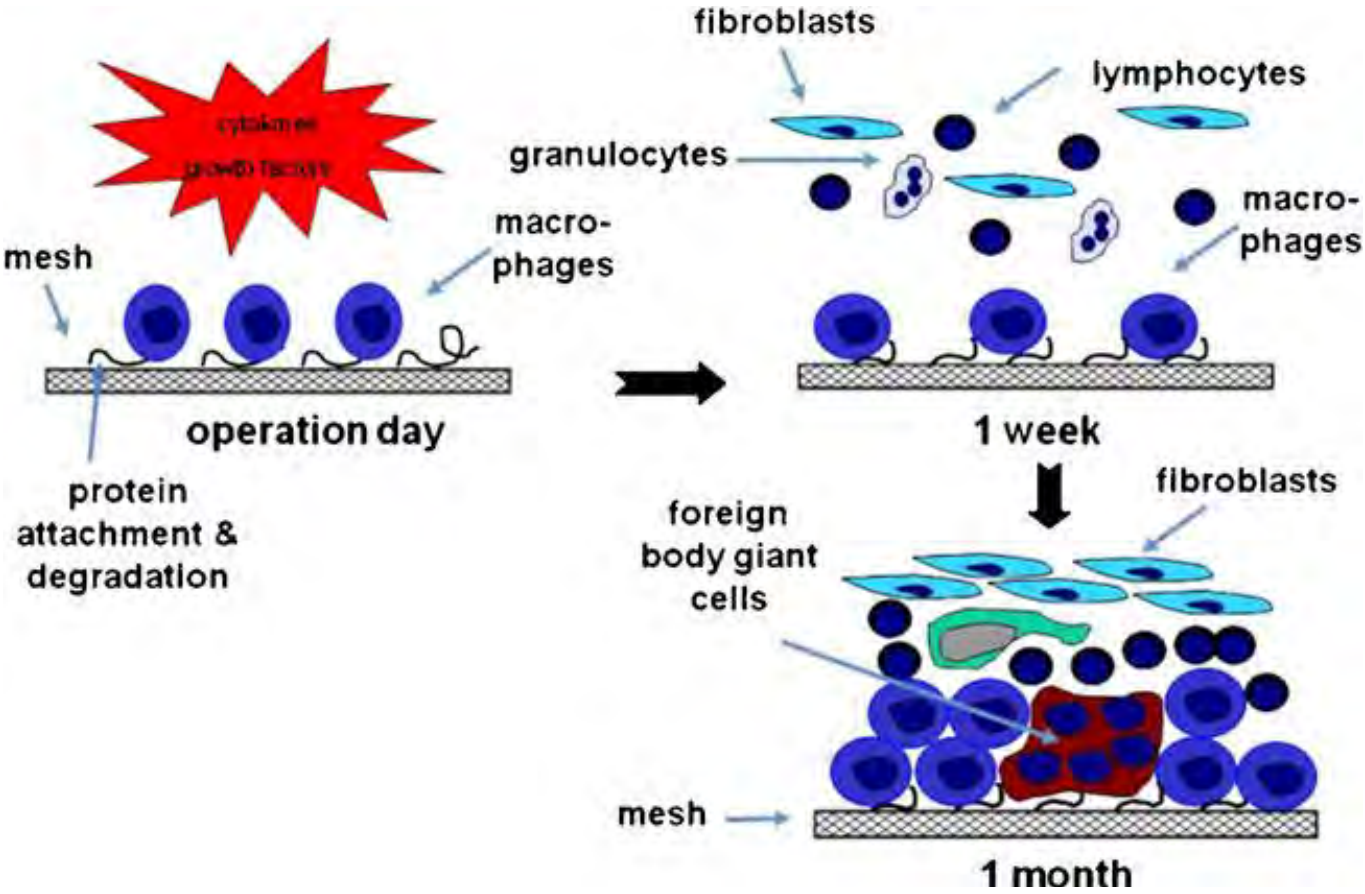


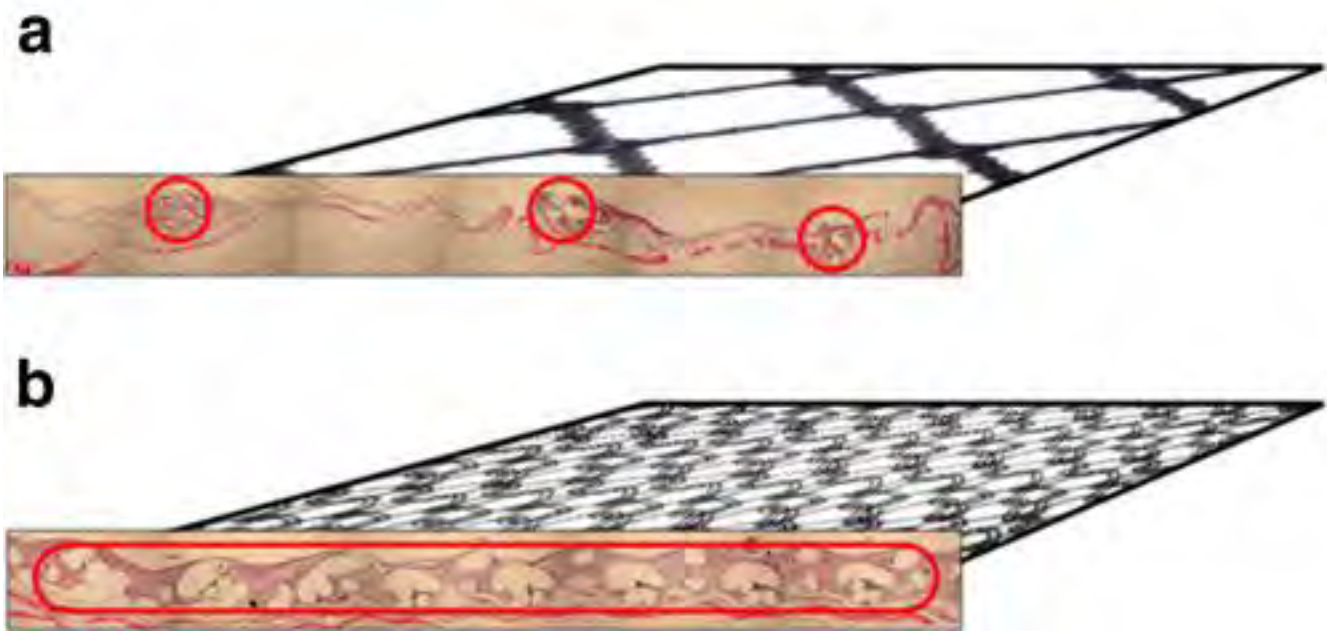
Fig. 1 Grab test at a textile mesh structure that never has been implanted, to illustrate the difficulty to characterise stability and elasticity by uniaxial measurements **a** without strain, **b** at a strain of 16 N, **c** complete release (images with courtesy of FEG Textiltechnik, Aachen)

Figure 6



Semin Immunopathol (2011) 33:235–243 - Formation of a foreign body granuloma at the mesh to host tissue interface

Figure 7



Semin Immunopathol (2011) 33:235–243 - a Scar net formation following large pore (~3 mm) and b scar plate formation following small-pore (~0.3 mm) mesh implantation

Figure 8

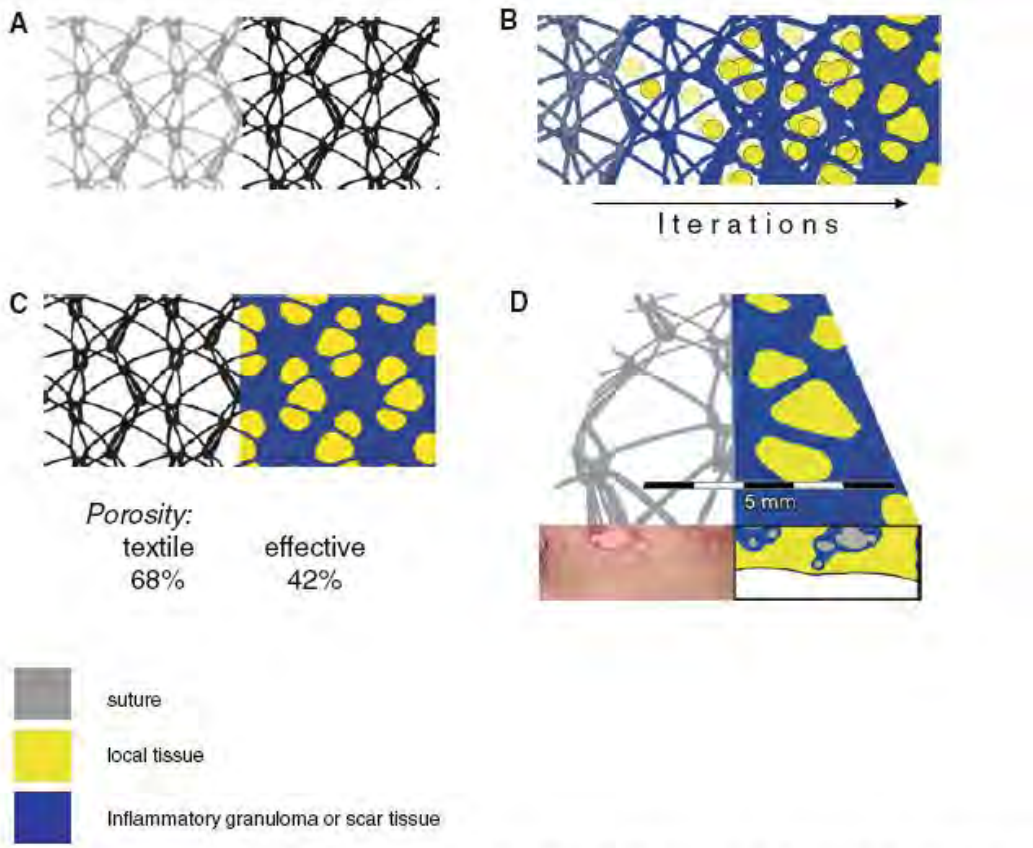
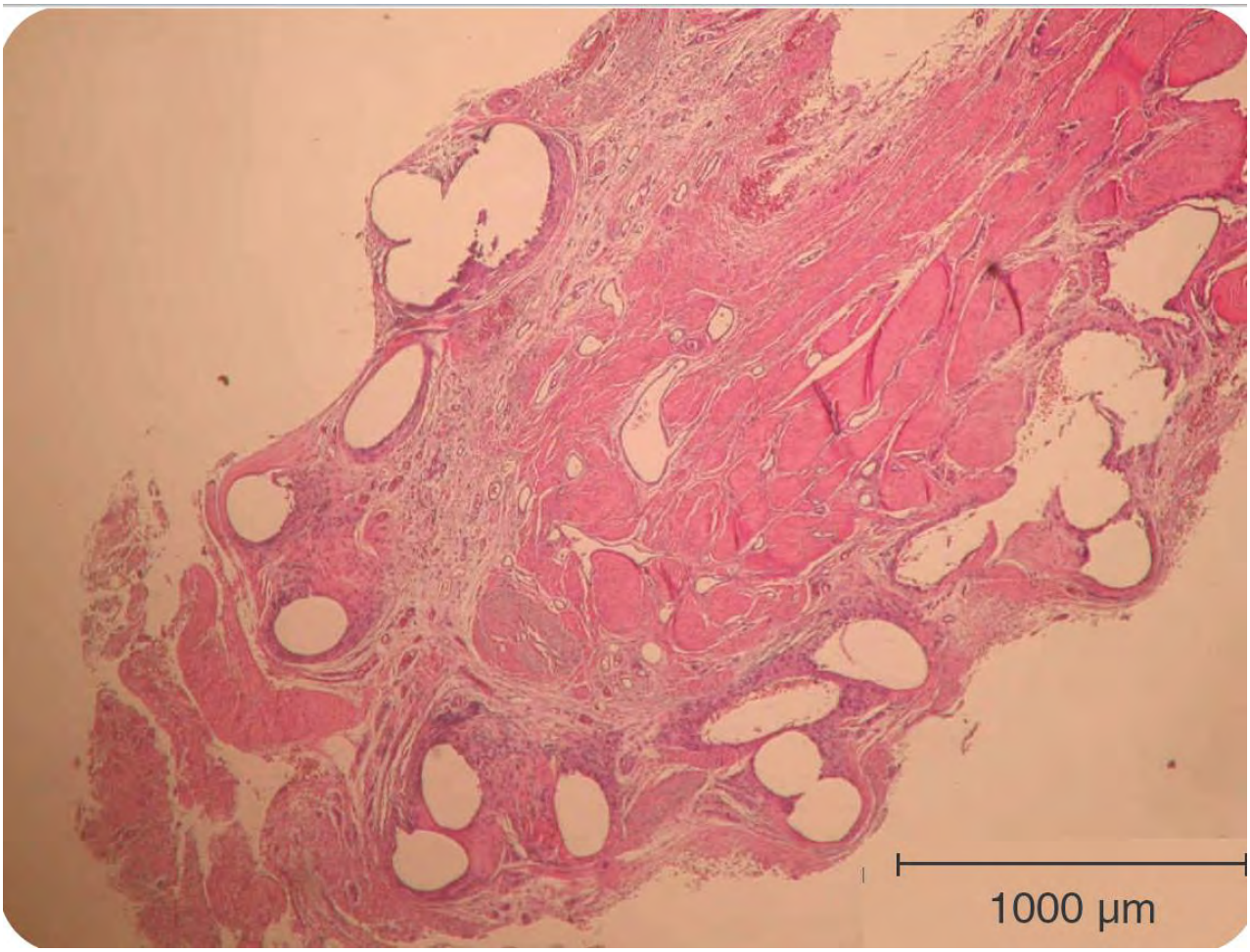


Fig. 2 Textile or effective porosity of surgical meshes and the extent of bridging after tissue incorporation **a** textile class I construction with large pores (*left*), where the textile porosity (*right*) reflects in a black/white image all the area that is not covered by the filaments as percentage of the entire mesh area, **b** calculation of effective porosity according to Mühl et al. [13] has to consider that polypropylene meshes need a circular interfilament distance of ≥1,000 µm [20] to avoid bridging. Identification of "good" pores (*yellow*) is done by iterative fitting of spheres with a diameter of 1,000 µm into the area, which is not covered by either the filaments or its foreign body granuloma. The resulting area as percentage of the entire mesh area reflects the effective porosity. **c** Large pore mesh with a textile porosity of 68 % and an effective porosity of 42 %. **d** Large pore mesh with "good" pores that does not induce bridging (HE staining) but recovered by filling the pores with local fat tissue only consideration of the pores geometry allows to identify small pore meshes despite high textile porosity and low weight, which showed more inflammation than a heavy-weight construction with bigger pores (Weyhe et al. [5])

Figure 9



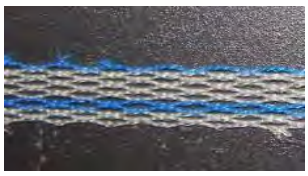
Tissue reaction and fibrotic ingrowth of polypropylene with roll up by scar shrinkage. Hematoxilin and eosin staining

Expert Rev. Med. Devices 4(3), (2007)

Figure 10

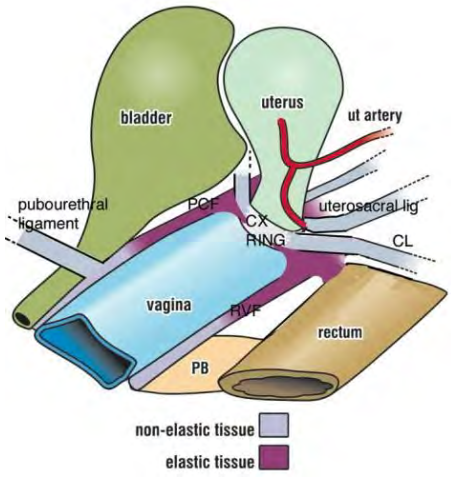
ETHICON Women's Health & Urology

There is no patient centric PF material !



macroscopic view of a blank mesh under uniaxial load of 1 N

microscopic view: reduced pore size due to collapsed pores

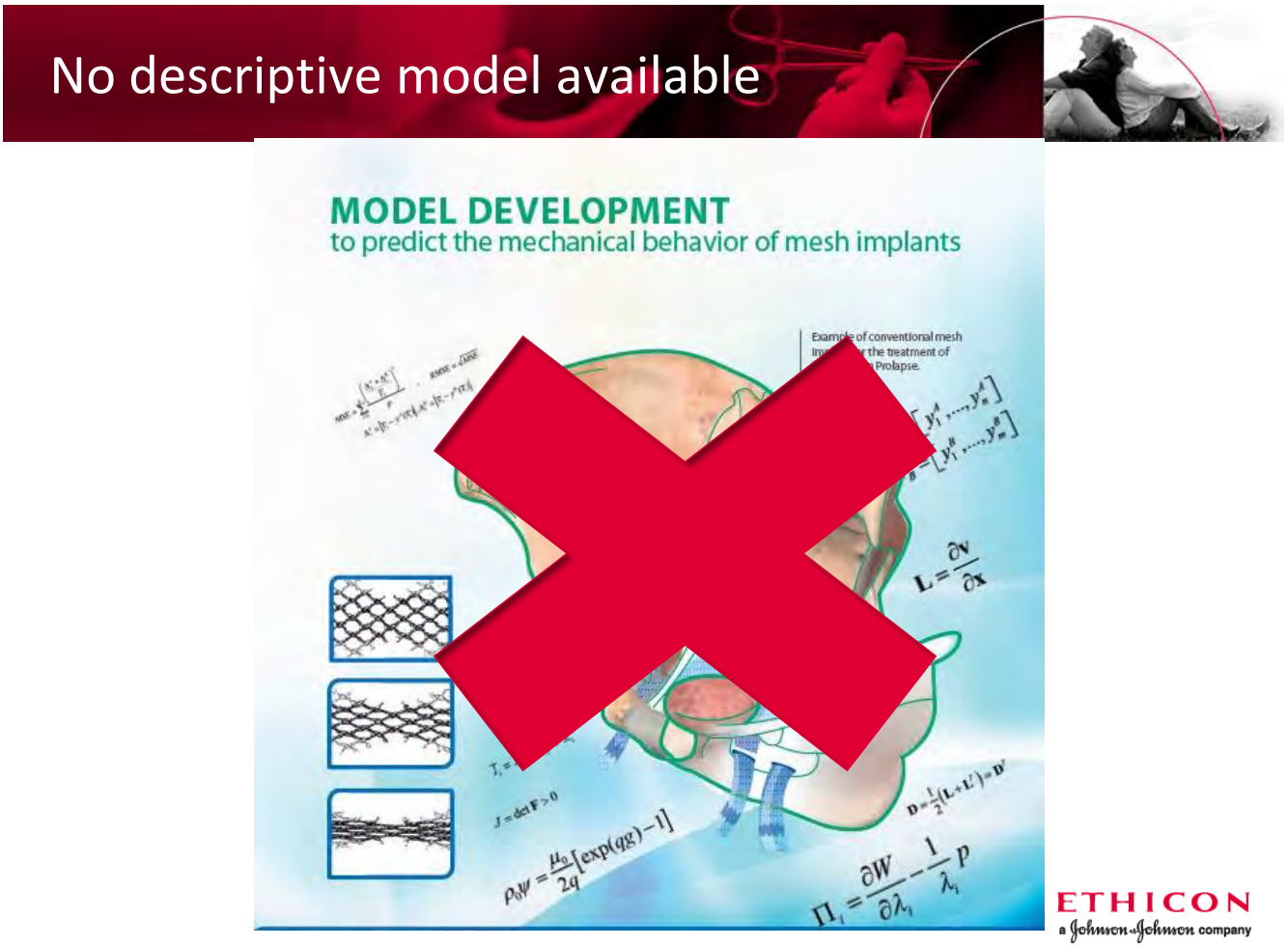


Stress shielding needed to avoid pore-collapse, deformation and pre-stretch

Different mechanical properties are needed in different area of PF

ETH.MESH.02227224: PowerPoint Presentation dtd 05/09/08 titled MGPP Thunder Decision Meeting

Figure 11



ETH.MESH.03753245: "Biomechanics" PowerPoint

Figure 12

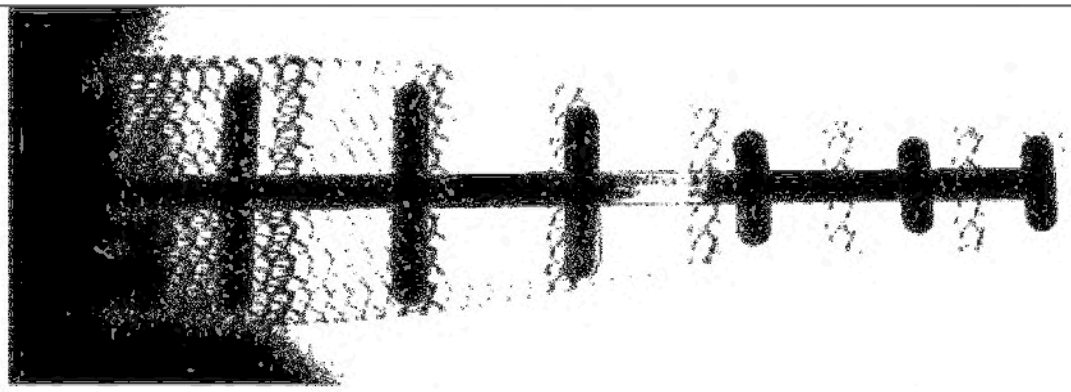


Figure 11 illustrates another possible stress-shielding concept consisting of an absorbable, laser cut, PDS-Film laminated onto the mesh. The PDS Film is bond to the mesh via a heat press process (120 °C, 20 s.). The in-vivo absorbable reinforcing element reduces the pore size kinematics effecting meshes under uniaxial load...

Figure 13

ETH.MESH.01782867: PowerPoint titled "Factors Related to Mesh Shrinkage" by Spychaj in 2007

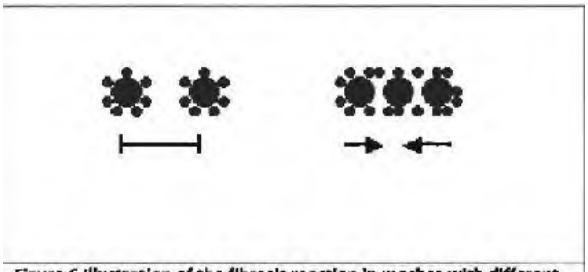
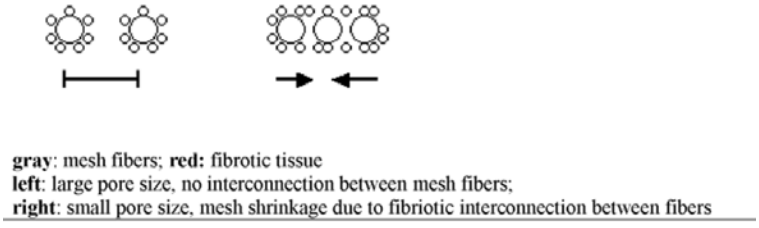


Figure 6 Illustration of the fibrosis reaction in meshes with different mesh sizes
gray: mesh fibers; red: fibrotic tissue
left: large pore size, no interconnection between mesh fibers;
right: small pore size, mesh shrinkage due to fibriotic interconnection between fibers

"Biomechanical consideration for Pelvic floor mesh design"



gray: mesh fibers; **red:** fibrotic tissue
left: large pore size, no interconnection between mesh fibers;
right: small pore size, mesh shrinkage due to fibriotic interconnection between fibers

June 2006 Expert Meeting

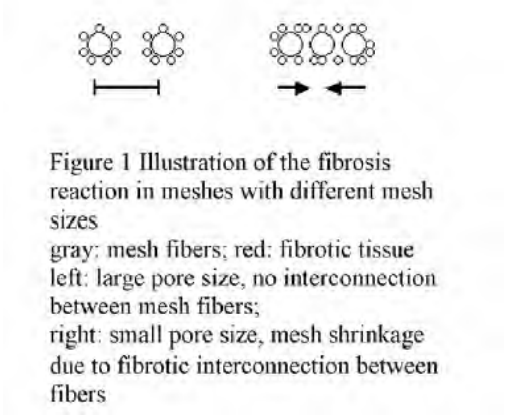
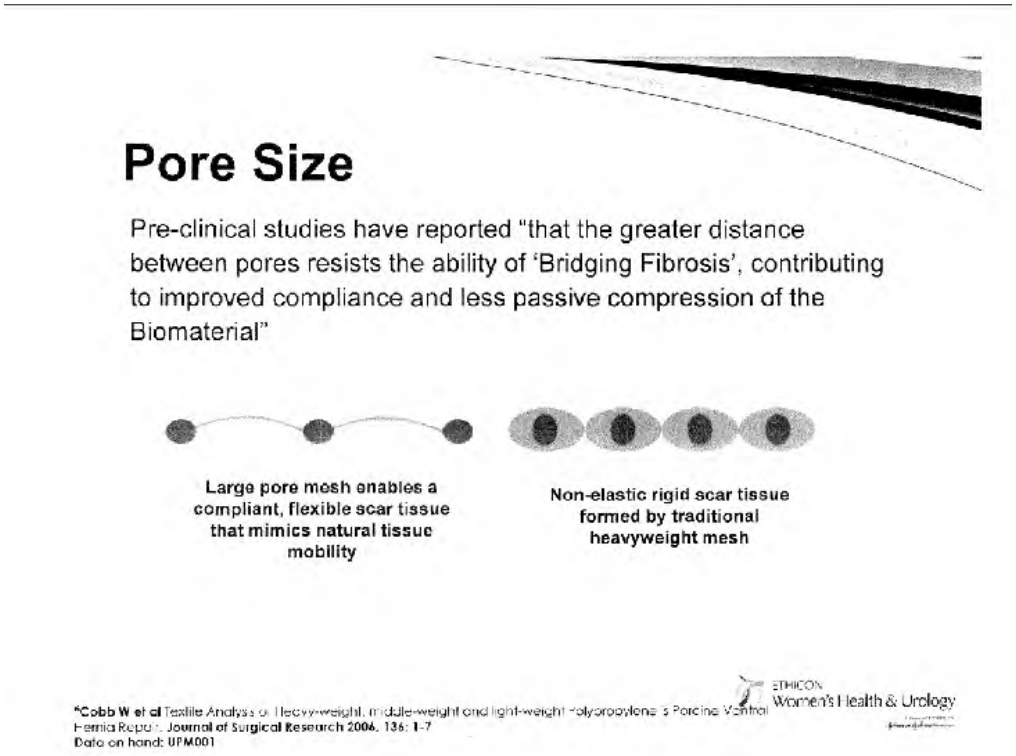


Figure 1 Illustration of the fibrosis reaction in meshes with different mesh sizes
gray: mesh fibers; red: fibrotic tissue
left: large pore size, no interconnection between mesh fibers;
right: small pore size, mesh shrinkage due to fibrotic interconnection between fibers

2006 Clinical Expert Report by David Robinson



ETH.MESH.002373968: PowerPoint titled "R&D Perspective – The Journey from Prolift to Prolift +M" by Volpe

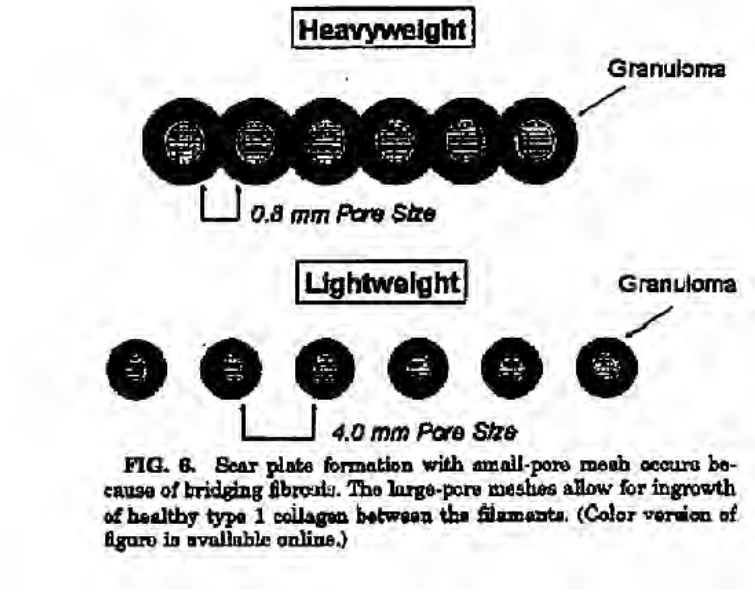


FIG. 6. Scar plate formation with small-pore mesh occurs because of bridging fibrosis. The large-pore meshes allow for ingrowth of healthy type 1 collagen between the filaments. (Color version of figure is available online.)

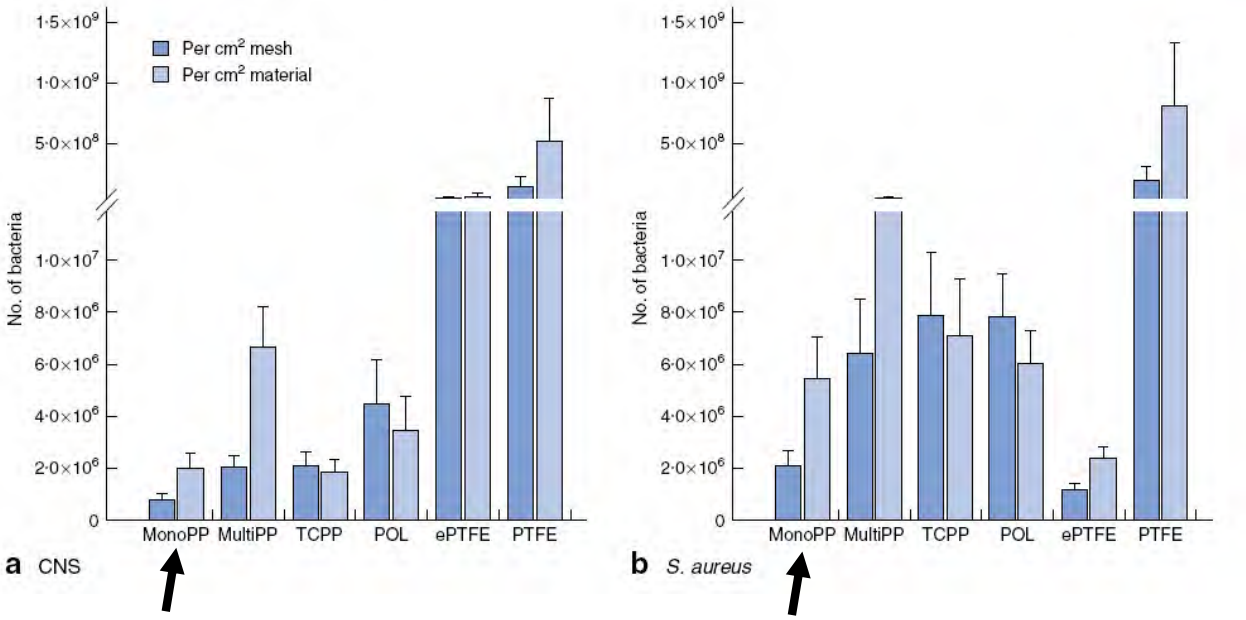
ETH-47802: Cobb WS, Burns JM, Peindl RD, Carbonell AM, Matthews BD, Kercher KW, Heniford BT *Textile analysis of heavyweight, mid-weight, and lightweight polypropylene mesh in a porcine ventral hernia model*.

Figure 14

Morphological aspects of surgical meshes as a risk factor for bacterial colonization

A. F. Engelsman[1,2], H. C. van der Mei[1], H. J. Busscher[1] and R. J. Ploeg[2]

British Journal of Surgery 2008; **95**: 1051–1059



Monofilament with smalles surface and least *S. aureus* !

Figure 15

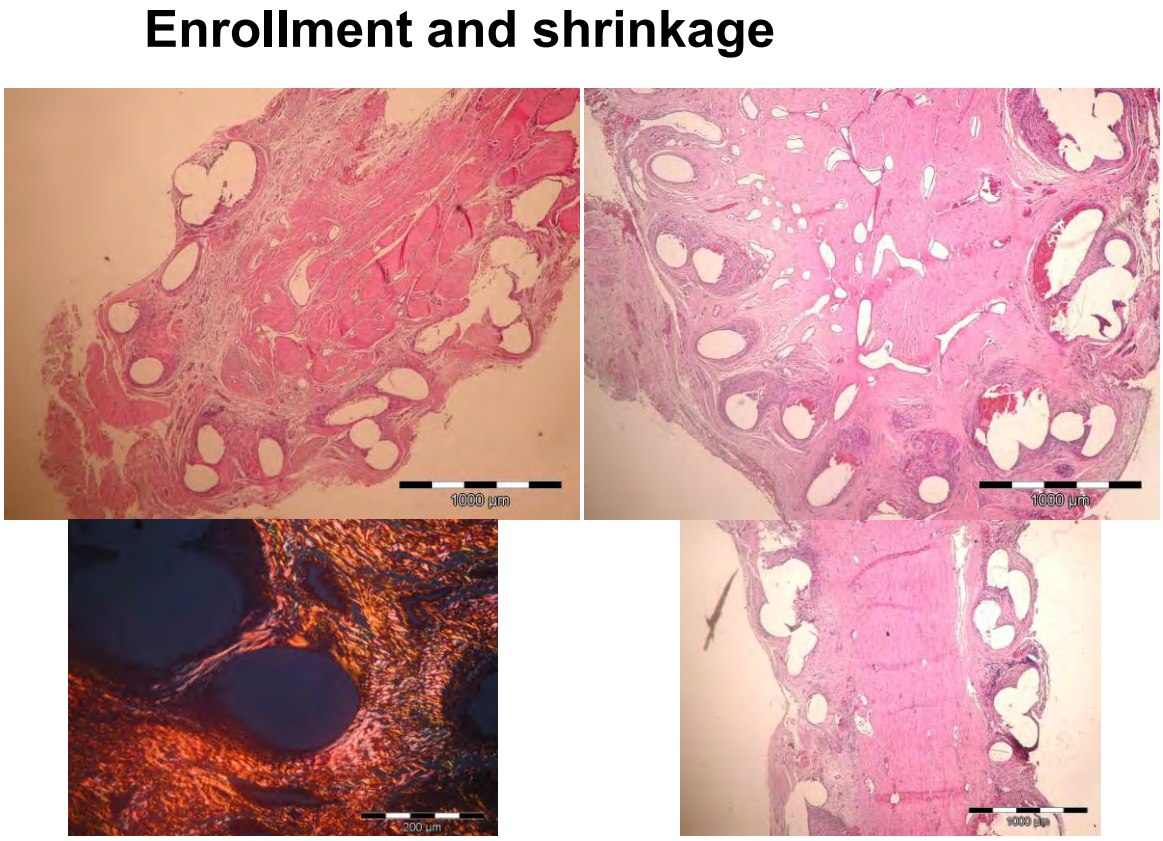


Figure 16

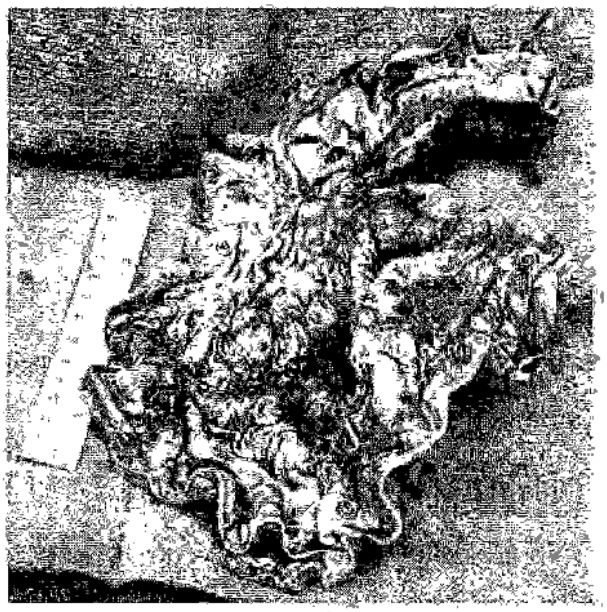
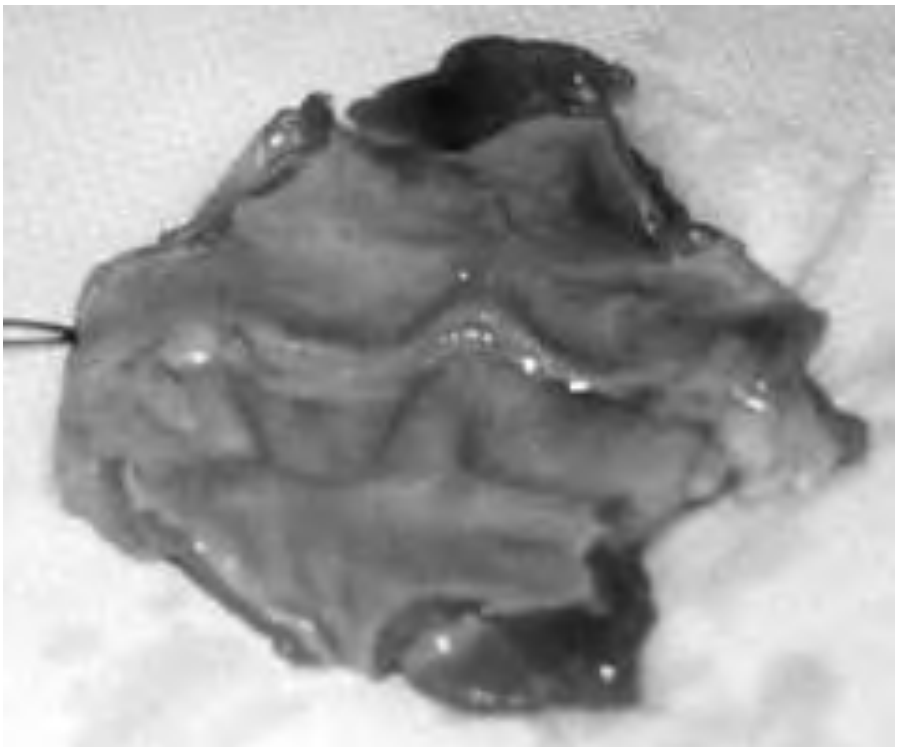


Figure 1. Kugel Composix hernia mesh immediately after explantation.

Costello CR, Bachman SL, Ramshaw BJ, Grant SA., *Materials characterization of explanted polypropylene hernia meshes*

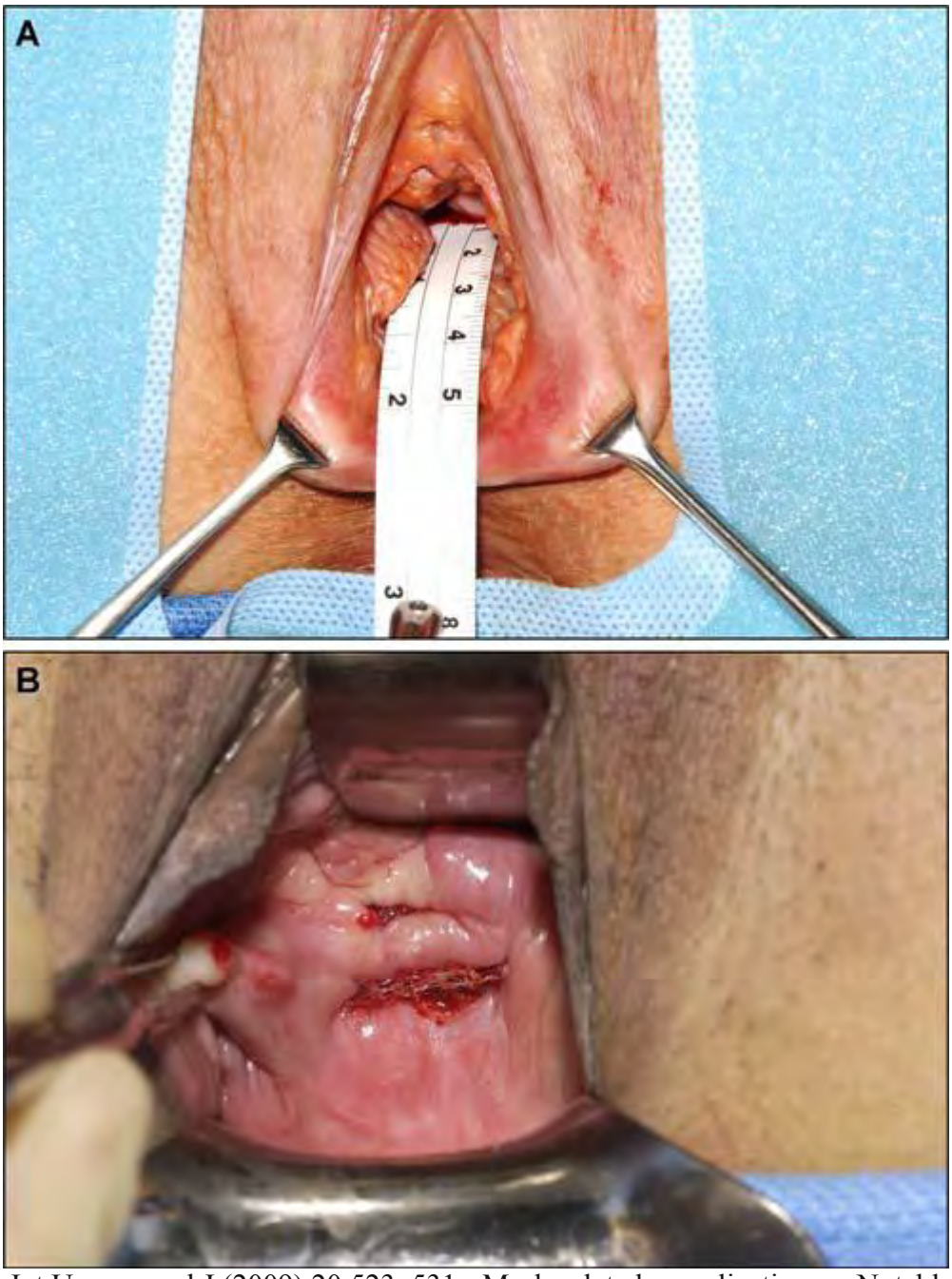
Explanted Prolift Mesh: Int Urogynecol J (2009) 20:523–531

Figure 27



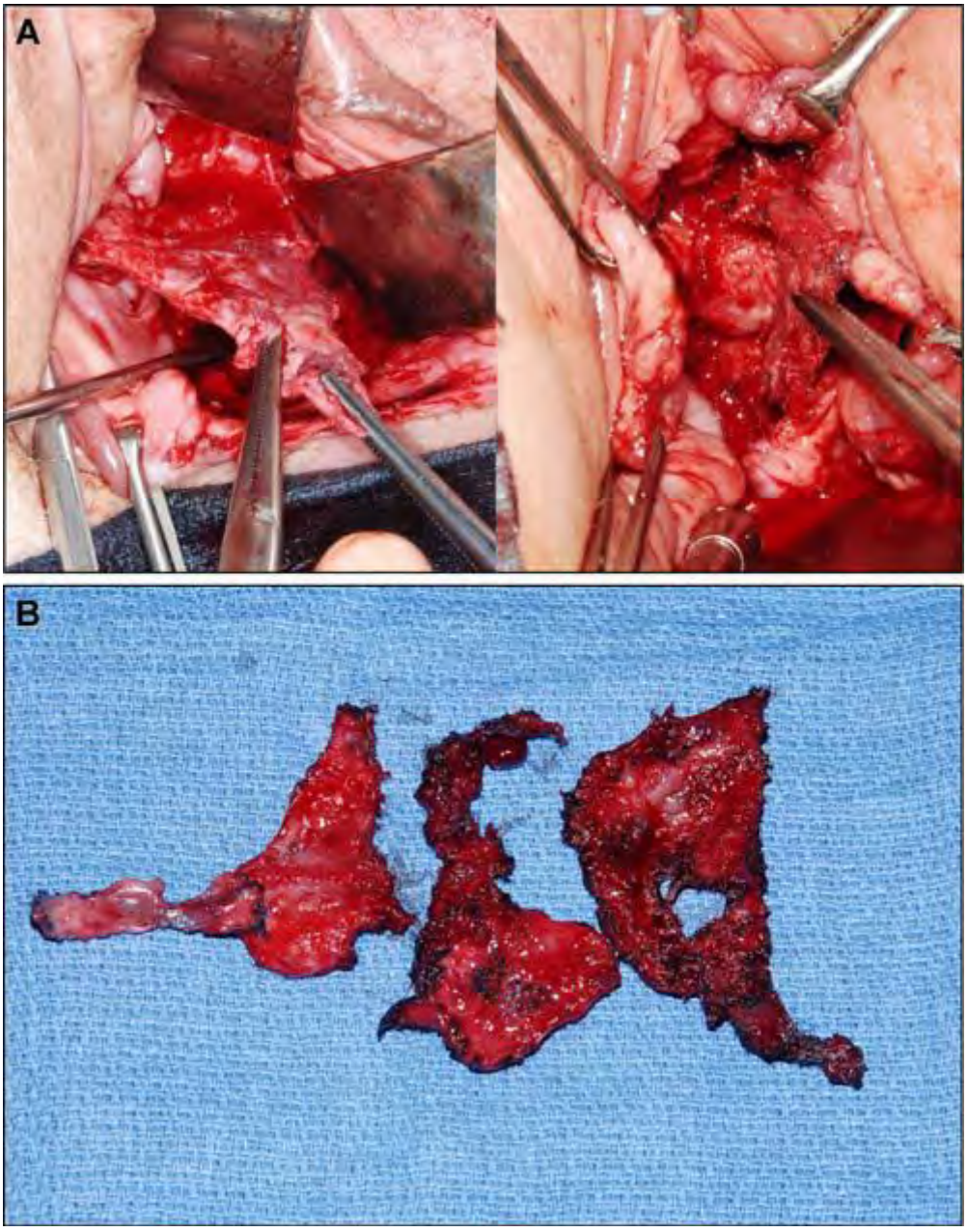
Klinge U, Klosterhalfen B, Muller M, Ottinger A, Schumpelick V. *Shrinking of Polypropylene Mesh in vivo: An Experimental Study in Dogs*

Figure 18



Int Urogynecol J (2009) 20:523–531 - Mesh-related complications. a Notable vaginal shortening, with total vaginal length of 4 cm, in a 48-year-old woman after vaginal hysterectomy, Prolift total pelvic floor repair, and tension-free vaginal tape. b Extensive anterior vaginal wall mesh erosion

Figure 19



Int Urogynecol J (2009) 20:523–531 - Vaginal mesh excision. a Photographs demonstrate complete vaginal excision of fibrous tissue and synthetic mesh from a 48-year old patient. b Excised vaginal mesh from the same patient